Infantile hemangiomas,
the implications of the changing landscape of treatment after propranolol

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Contents

List of email addresses related to the thesis

- www.hecovan.nl
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- www.kinderformularium.nl

List of abbreviations

ACE	angiotensin converting enzyme
AT	angiotensin
bFGF	basic fibroblast growth factor
cAPM	cyclic adenosine monophosphate
CCR-6	chemokine receptor 6
CD	cluster of differentiation
CO_2	carbon dioxide
CT	computed tomography
CVS	chorionic villus sampling
D3	type-3 iodothyronine deiodinase
3D	3-dimensional
ECG	electrocardiography
ENT	ear nose and throat
EPC	endothelial progenitor cell
GFS	gel forming solution
GLUT1	glucose transporter protein type 1 (GLUT1)
HCM	hypertrophic cardiomyopathy
Hevas	ouder- en patiëntvereniging voor Hemangiomen en Vasculaire malformaties
HIF-1α	hypoxia inducible factor-1α
HSS	hemangioma severity scale
IDO	indoleamine 2,3-dioxygenase
IGF-2	insulin-like growth factor 2
IH	infantile hemangioma
ISSVA	International Society for the Study of Vascular Anomalies
KHE	Kaposiform hemangioendothelioma
KMP	Kasabach-Merritt phenomenon
LV	left ventricle
MMP	matrix metalloproteinase
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
Nd-Yag	neodymium-doped yttrium aluminum garnet
NICH	non-involuting congenital hemangioma
OCS	oral corticosteroids
PDL	pulsed dye laser
QoL	quality of life
RAS	renin-angiotensin system
RICH	rapidly involuting congenital hemangioma
RUNMC	Radboud University Nijmegen Medical Centre
SD	standard deviation
SPECT	single photon emission computed tomography
SPSS	statistical package for the social sciences
TA	tufted angioma
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VSD	ventricular septal defect
WMO	Wet medisch-wetenschappelijk onderzoek met mensen

1

General introduction and outline

1.1 An introduction to hemangioma

1.1.1 Classification

In ancient medical literature the word 'hemangioma' was used to describe a wide range of vascular tumors and malformations, resulting in indistinctness concerning diagnosis and prognosis. In current literature, as well as in this thesis, the term 'infantile hemangioma' (IH) is used to make a distinction with other vascular anomalies.

According to the classification of the International Society for the Study of Vascular Anomalies (ISSVA), vascular anomalies may be mainly classified as vascular tumors and vascular malformations, based on differences in biologic and cellular characteristics as well as the natural course of the lesion.[1] Infantile hemangioma belongs to the group of vascular tumors and is a true neoplastic proliferation of endothelial cells with characteristic early natural history of growth, followed by spontaneous involution over years. Vascular malformations on the other hand are structurally abnormal vessels arising from errors in embryogenesis, have normal endothelial cell turnover and do not involute spontaneously. Unlike other vascular anomalies, IH cells express a unique immunohistochemical phenotype that includes glucose transporter protein type 1 (GLUT1) at all stages of development.[2]

1.1.2 Epidemiology and genetics

Although the exact prevalence is difficult to determine,[3] IH is estimated to occur in about 3-10% of the Caucasian infants and is therefore the most common benign tumor of childhood.[4,5] Low birth weight (less than 1500 gram) appears to be the most significant risk factor for IH development according to multivariate analysis. Other risk factors for the development of IH are female sex, with a sex ratio ranging from 3:1 to 5:1, Caucasian race, prematurity, family history of IH and newborns from multiple gestations. Perinatal associations include older maternal age, placenta previa and pre-eclampsia. Infants from women who have undergone transcervical chorionic villus sampling (CVS) also seem to have an increased risk for developing IHs as opposed to other prenatal diagnostics like transabdominal CVS and amniotic fluid puncture.[6,7]

The vast majority of IH occurs sporadically; in less than 10% of the IH patients there is a marked family history of IH.[8] In a small number of these families, IH segregates as a highly penetrant autosomal trait.[9] Gene linkage studies of familial IH show evidence of linkage to chromosome 5q31-33.[10] On the other hand, it could be concluded in twin studies, that hereditary factors were not principal causes of IH.[11]

1.1.3 Clinical phenotypes

During the growth phase, IHs are in general firm and elastic tumors, irrespective of the clinical subtype. They are slightly warm but not pulsatile on palpation and painless, except in case of ulceration.[12] The clinical appearance of the IH is variable, depending on the

infiltration depth of the tumor within the skin. The most common superficial IHs (50-60%), located in the superficial dermis, are bright red and lobulated. Deep IHs comprising 15% of all IHs, on the other hand, arise in the reticular dermis or subcutis and emerge as raised soft masses, often with a bluish shine. Not uncommonly, IHs have both superficial and deep features (25-35%) and are called mixed IHs.[13]

Besides, each IH can be subclassified according to the size, the anatomic localization and the morphologic subtype:

- The size of the IH may vary significantly, ranging from pinhead large to the involvement of an entire limb. In most cases (80%) however, IHs are less than 3 cm in diameter.[14]
- For unknown reasons, the anatomic localization mainly includes the face (40%) and neck (20%).[14] On the other hand, IHs can appear anywhere on the body and may even affect internal organs, in most cases the liver.[15]
- In addition, four different morphologic subtypes can be recognized. The first and most common are localized IHs with a focal tumor-like aspect. The second are segmental IHs with a more plaque-like distribution involving a region of skin and are more often associated with complications. Undeterminated IHs are the third type and not always distinguished as a separate subgroup in literature, but correspond to IHs with a segmental distribution but without clear circumscription. The last subtype; multifocal IHs, are sometimes associated with visceral involvement.[12]

Figure 1
Superficial, localized IH
Age of the patient: 3.5 months

Figure 2
Superficial, segmental IH
Age of the patient: 1 month

1.1.4 Natural history

Infantile hemangiomas are unique and distinctive with respect to their natural growth characteristics. Because of the enormously variable spectrum of severity, from tiny, banal to large and risky lesions, the prediction of natural behavior and prognosis of the IH in the

Figure 3
Deep IH
Age of the patient: 8 months

Figure 4
Mixed IH
Age of the patient: 4.5 months

individual patient is difficult. Nevertheless, a pattern of the growth characteristics of IH in phases is discernible. The distinct growth phases are: nascent, proliferating, involuting and involuted.[16] In approximately 50% of the neonates in whom an IH develops, a precursor lesion is present at birth.[17] These nascent lesions appear most frequently as a telangiectatic macule with a pale halo or as a pale or an erythematous macule.[18] In the first days or weeks after birth, the IH appears and grows disproportionally whereby the growth phase comprises the first 3-6 months,[14] but may extend until the 9th to 12th month in IHs with a subcutaneous component.[12] In exceptional cases, this growth phase may continue until 24 months.[19] The growth of the IH in general implicates no significant increase of the primarily affected surface area, but merely a thickening and thereby an increase in volume of the tumor. Following this growth phase, most IHs stabilize spontaneously, and regress over several months or years.[12] The median age at the end of the involution phase is about 4 years.[20]

After involution, residual lesions such as telangiectasias, skin atrophy, skin surplus, scarring and/or fibrofatty tissue may remain. It seems that epidermal invasion is a predictor for these residual lesions.[20]

1.1.5 Pathology

Histologically, proliferating IHs are composed of masses of compact capillaries lined by plump endothelial cells with increased mitotic rates.[21] In addition to endothelial cells, IHs are also composed of stromal components, including fibroblasts, pericytes and mast cells.[22,23] As the lesion involutes, mitosis gradually decreases with increased apoptosis of endothelial cells and gradual replacement of vascular tissue by fibrofatty tissue.

1.1.6 Pathogenesis

Despite their frequency, the etiology of IH has only just started to be elucidated. At this time, there are three partially competing, but in some way complimentary, hypotheses of underlying developmental mechanisms.

a) Embolization of placental endothelial cells

A great similarity between immunohistochemical markers of IH and human placental microvessels is demonstrated (GLUT1, Lewis Y antigen, merosin, chemokine receptor 6 (CCR-6), CD15, indoleamine 2,3-dioxygenase (IDO)).[2] This immunohistochemical profile differentiates IH from other vascular tumors. Infantile hemangioma endothelial cells have also been found to express other types of molecules normally found in placenta, including type-3 iodothyronine deiodinase (D3) and insulin-like growth factor 2 (IGF-2).[24-26] In line with these findings is the high level of genetic similarity between placenta and IH.[27] With this knowledge, it was hypothesized that embolization of placental endothelial cells to the fetus could play a role in the pathogenesis of IH. In favor of this hypothesis is the finding that chorionic villus sampling is associated with an increased incidence of IH.[28] But subsequent molecular genetic investigation could not reveal evidence for maternal-fetal microchimerism in children with a solitary IH. This however does not rule out the possibility of placental origin of IH tissue, because the placenta is predominantly fetal in origin.[29,30] It also remains to be explored whether or not this applies to diffuse neonatal hemangiomatosis as well, which is characterized by numerous cutaneous and visceral IHs, and associated with placental hemangiomas (chorangiomas).[6]

b) Increased angiogenic and vasculogenic activity

Angiogenic peptides, like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and their receptors, are largely involved in endothelial cell regulation and the growth of IH. Mutations in key growth regulatory pathways might play a role in the clonal expansion of endothelial cells in IH. Somatically acquired mutations in the VEGF receptors have been found in histological specimens of some IH patients and this point may lead to abnormal endothelial cell proliferation as a result of dysregulated VEGF signaling. Expression of vascular endothelial growth factor receptor 1 (VEGFR1) is reduced in IH endothelial cells, resulting in VEGF-induced activation of VEGFR2 and downstream signaling pathways, leading to stimulation of angiogenesis.[31]

As opposed to the previous thoughts, vasculogenesis, in addition to stimulated angiogenesis, is relevant in the pathogenesis of IH as well. Endothelial progenitor cells (EPCs) are vascular stem cells with the potential to contribute to postnatal vascular development. At the present time, there is compelling evidence that IH arises from bone marrow-derived EPCs, capable of inducing postnatal formation of vascular tissue.[32,33] A subset of progenitor cells possessing the surface markers CD34+ and CD133+ could be isolated from IH tissues. These EPCs have been shown to differentiate into endothelial cells

in vitro[34] and are increased 15-fold in IH compared to controls.[35] Several mediators of EPC trafficking and vasculogenesis, such as VEGF-A and hypoxia inducible factor-1α (HIF-1α), were found to be elevated in blood and IH specimens taken from IH patients.[36] A major breakthrough was the development of an IH animal model by injecting immune-deficient mice with CD133+ EPCs. The development of GLUT1+ vascular tumors in these mice highlighted the importance of CD133+ EPCs in the pathophysiology of IH and was an important impulse for the study of mechanisms of action of drugs used in IH.[37,38]

c) Tissue hypoxia

Tissue hypoxia seems to be the most influential inducer of angiogenesis (and vasculogenesis). In literature an association between placental hypoxia and IH has been described.[39,40] The inverse relationship between birth weight and IH incidence[41] and the association of IH with retinopathy of prematurity are indications in the same direction.[42] Hypoxic environment triggers the production of the transcription factor HIF-1α, regulating genes enhancing angiogenesis such as VEGF-A, IGF-2 and GLUT1.[43-45] Hypoxia can also trigger angiogenesis by stimulating the secretion of pro-angiogenetic molecules from myeloid cells in IH.[46]

Given the giant variability in IHs, it is likely that the pathogenesis of IH will not be restricted to one, but to a combination of genetic and environmental factors.[47]

1.1.7 IH associated with structural anomalies

The two main clinical variants in which the IH can give an indication of an underlying anomaly are: large, flat, facial IHs with a segmental distribution (typically 5 cm in diameter or larger) and medium to large sized IHs involving the lumbosacral or perineal region.

The first one is associated with PHACES syndrome (posterior fossa malformations, hemangioma, arterial anomalies, cardiac anomalies, eye abnormalities and sternal defects), an uncommon but not rare cutaneous neurovascular syndrome. The exact incidence of PHACES among patients with large IH in the head and neck region is unknown but has previously been estimated at 20-30%, with cerebrovascular and cardiac anomalies being the most common extra-cutaneous associations.[48,49] Particularly the IH in the frontotemporal and frontonasal segments of the face correlate with an increased risk of this association.[48] For these patients, cerebral magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) and careful cardiac and ophthalmological examination is indicated.[49]

Infantile hemangiomas overlying the lumbosacral skin or perineum can also be associated with underlying structural anomalies like tethered spinal cord. The structural anomalies in this region have been referred to by different acronyms, highlighting similar associations: LUMBAR[50] (lower body hemangioma and other cutaneous defects, urogenital abnormalities, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies and renal anomalies), SACRAL[51] and PELVIS.[52] Screening MRI of the spine is

recommended for children with these lesions. For children younger than three months, MRI may not be sensitive enough and in asymptomatic cases, this imaging study may best be postponed till approximately three to six months of age. Before this age, ultrasonography of the spine, abdomen and pelvis with color Doppler is in the first instance recommended.[50,53]

1.1.8 Differential Diagnosis

The diagnosis of IH is usually easily made on clinical findings. Nevertheless IHs share many characteristics with other benign and malignant vascular anomalies.[54,55] Incorrect diagnosis may lead to significant errors in management as well as in prognostic information given to patients and/or their parents. In some atypical cases, duplex ultrasonography or a biopsy should therefore be performed to exclude other soft tissue tumors or vascular anomalies.[12] The differential diagnosis of IH is very extensive, associated with the variability in clinical aspect (Table 1). A selection of the most important differential diagnoses, relevant for this thesis, is described below.

- *Congenital hemangioma*
  These vascular tumors are fully-grown at birth in contrast to IHs. Congenital hemangiomas can be divided into rapidly involuting (RICH) and non-involuting (NICH) subsets, on the basis of their clinical behavior. The lack of GLUT1 staining may be helpful to distinguish these tumors from IHs, but the clinical aspect and ultrasound aspect is often so distinctive that a biopsy is not required.[54,56]

- *Tufted angioma and Kaposiform hemangioendothelioma*
  Tufted angioma (TA) is an uncommon, benign vascular tumor of the skin with a variable clinical presentation. The etiology and pathogenesis has not been fully elucidated. Most TA are acquired early in infancy but are typically not noted at time of birth. Three distinguishing features can be helpful: the firm aspect of the tumor, the presence of localized pain and increased hair growth.[57]
  Kaposiform hemangioendothelioma (KHE) is a vascular tumor that is present at birth or may develop in early childhood. Lesions of KHE may be more deeply infiltrated than IH or TA. Because of the clinical and histological overlap of KHE and TA, a spectrum of disease is suggested. Both TA and KHE can be associated with Kasabach-Merritt phenomenon (KMP), characterized by clinically significant and life-threatening thrombocytopenia in the presence of a TA or more often a KHE. The primary process behind the KMP is platelet-trapping within the tumor.[58]

1.1.9 Imaging

More than 90% of vascular anomalies can be classified as IHs or vascular malformations by only taking history and performing physical examination.[16] Imaging studies are rarely

Table 1 Main differential diagnosis of IH

***Congenital* Anomaly**
Vascular tumor or malformation
Congenital hemangioma RICH type
Congenital hemangioma NICH type
Kaposiform hemangioendothelioma
Tufted angioma
Port-wine stain
Macrocystic lymphatic malformation
Venous malformation
Others
Myofibromatosis
Dermoid cyst
Teratoma
Sarcoma (fibrosarcoma)
Neuroblastoma
Leukemia (blue berry muffin baby)
Tumor or anomaly developed *after* birth
Vascular tumor or malformation
Pyogenic granuloma (especially on the face)
Macrocystic lymphatic malformation
Glomuvenous and venous malformation
Hemangioendothelioma
Others
Hematoma
Benign tumors (pilomatrixoma, Spitz naevus, myofibromatosis, neurofibroma, eosinophilic granuloma, myxoma, lipoblastoma….)
Malignant tumors (sarcoma, lymphoma, cutaneous localization of neuroblastoma or leukemia)

Modified from Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: Part I Pathophysiology, epidemiology, clinical features, life cycle and associated structural abnormalities J Eur Acad Dermatol Venereol 2011; 25: 1245-1253.[12]

necessary, except for cases in which the diagnosis is unclear or in which the extent of the lesion is difficult to assess. Further investigation may also be required to rule out concomitant lesions and other associated abnormalities.[59]

Duplex ultrasonography is the least invasive and most cost-effective imaging modality for IH and recommended as the initial test of choice to differentiate between

vascular tumors and malformations.[60,61] It is useful for distinguishing deep IHs from other entities like venous malformations, because it typically shows combined high and low flow. Duplex ultrasonography is however highly operator dependent and it fails sometimes in assessing the extent of the lesion and presence of other anomalies.[62]
Computed tomography (CT) or MRI are superior in delineating the extent of the lesion.[62] For volume measurement of IH in daily practice, these imaging studies are only moderately suitable because they are not immediately available, costly and require sedation or general anesthesia in young infants.[60]

Besides, several bedside techniques have been described for estimating IH volume, assuming that IHs are perfectly dome shaped.[63-65] These methods are not suitable for irregular shaped IHs and have an inevitable inter-observer variation. Until now, in most studies, two-dimensional photographs have been used to follow up the evolution of the IH. This method is however not appropriate for objective assessment of growth and involution, in the first place because IH proliferation generally implicates thickening of the IH without increase of the affected surface area, and in the second place because of a great inter-observer variation. Objective ways, like three-dimensional (3D) imaging, to measure growth and involution of IH are important, for monitoring patients in routine clinical practice and evaluating treatment efficacy in clinical studies.[65]

1.2 Complications and treatment indications for IH

In relation to their natural history, characterized by spontaneous involution, most IHs do not require therapeutic intervention and the policy of active non-intervention is legitimized. However, 10-15% of the IHs potentially result in serious complications which should be anticipated, because treatment options do exist.[66] The IHs requiring special attention will be described in the following four sections.

1.2.1 Vital risk

Infantile hemangiomas associated with potentially life-threatening complications are rare. But particularly IHs affecting the airway or liver, as well as extensive IHs, may lead to life-threatening emergencies.

- Airway IHs are notorious for their morbidity and mortality in young infants. A cutaneous IH in a mandibular distribution ('beard' region) is a marker for a high risk of airway IH.[62] In clinical practice however, skin lesions may be absent and airway IHs may be unpredictable and unexpectedly revealed during 'routine' bronchoscopy for evaluating respiratory distress. Although subglottic IHs are more emphasized in literature, IH may occur anywhere throughout the airway. Clinicians should be alert of signs and symptoms that could indicate an airway IH, especially hoarse cry, stridor or noisy breathing. Prompt referral to pediatric otolaryngology is imperative to directly evaluate the airway and

start treatment as early as possible if necessary, perhaps even before laryngoscopy has been performed.[67]

- The liver is the most common extra-cutaneous site of IH involvement. Hepatic hemangiomatosis is usually associated with multifocal IHs, especially more than 5 IHs on the skin, particularly of pinhead size and called diffuse neonatal hemangiomatosis or multifocal IHs with extra-cutaneous disease. The innocuous variant, benign cutaneous hemangiomatosis or multifocal IHs without extra-cutaneous disease, is characterized by identical cutaneous IHs but without visceral involvement.[68] Liver ultrasonography with Doppler flow assessment of the hepatic blood flow is useful in diagnosing hepatic involvement. If liver IHs are present, small and asymptomatic, serial ultrasonography is adequate for follow-up.[69] Much less frequently, liver IHs can cause severe liver enlargement and/or high-output cardiac failure with possibly consumptive hypothyroidism.[70] The last is probably associated with the high level of type-3 iodothyronine deiodinase-activity found in IH tissue, normally expressed in the brain and placenta and involved in the inactivation of thyroxine. It is therefore postulated that in a large growing IH, increased inactivation of thyroxine exceeds the normal production capacity of the thyroid, clinically resulting in hypothyroidism.[24]
- Large, voluminous cutaneous IH can be complicated by high-output cardiac failure, resulting from increased vascular flow.[66]

1.2.2 Painful or extensive ulceration

Ulceration is the most common complication of IH, occurring in about 15-25% of the IH in referral centers.[67,71] It is the most common reason for IH referral to specialists, since it causes pain, resulting in parental concern. Besides pain, ulceration can cause some other significant complications including infection, bleeding and more commonly eventual scarring and disfigurement. Ulceration most commonly occurs during the peak of IH proliferation. The pathogenesis of ulceration is not completely clarified, however three main factors may play a role. In the first place sites of trauma (maceration, friction or both), in the second place local factors like bacteria (infection or colonization) and in the last place tissue hypoxia, such that ulceration occurs when an IH outgrows its own blood supply.[62]

1.2.3 Functional risk

Infantile hemangiomas can lead to functional impairment in many different ways; location in periorificial areas constitutes the largest group. Most common are the periorbital IHs, possibly threatening vision development. Amblyopia is the most common complication associated with periorbital IHs and in general, three major causes can be differentiated. Anisometropia is the first and most common cause of amblyopia. In IH patients, this anisometropia generally results from induced astigmatism or myopia due to direct pressure of the tumor on the eye. The second way amblyopia can be induced is by visual

Figure 5
Superficial, localized ulcerating IH
Age of the patient: 3 months

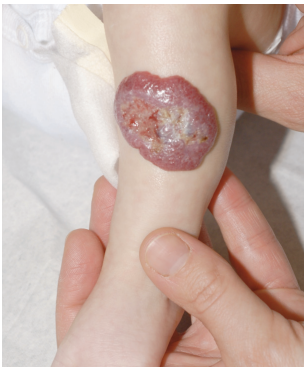

Figure 6
Superficial, localized ulcerating IH
Age of the patient: 3 months

deprivation secondary to occlusion of the visual axis duo the mass effect of the IH itself or induced ptosis from the IH. Strabismus is the third cause of amblyopia, resulting from a mass effect of the IH or due to direct involvement of the extra-ocular muscles.[72]

Other potential complications of periorbital IHs include myopia, tear duct obstruction, proptosis and ptosis. To prevent loss of vision, any infant with a periorbital IH should be referred early to an ophthalmologist, familiar with these issues, for evaluation.[16]

Other examples of worrying functional impairment include oral IHs, with lip involvement, in which an indurated swelling may interfere with the suction ring and adversely affect feeding, in particular in case of painful ulceration. Nasal IHs can cover the nostrils and threaten underlying cartilage tissue in case of necrosis or extensive growth. Infantile hemangiomas of the ear can result in ear infection, closure of the ear canal and subsequent conductive hearing loss. In addition, large IHs located on the head and neck, may lead to positional torticollis and/or plagiocephaly.[66,67]

1.2.4 Aesthetic risk/psychosocial risk

The perception that IH may lead to permanent disfigurement has increased significantly in the past decades and is becoming an increasingly important reason for initiation of treatment. There are numerous IHs that may lead to significant aesthetic problems as a result of their location, size or shape. Large facial IHs, occupying a significant region of skin may cause significant cosmetic concern, both in the growth and involution phase but also after involution, in case of significant residual lesions. Also smaller facial IHs, particularly on the central face or involving contoured surfaces, for example the nasal tip or lip, can result in significant cosmetic sequelae. When poor aesthetic outcome is anticipated, intervention

should be considered as soon as possible, with the physician weighing risks and benefits of the specific treatments.

On the other hand, in present times, physicians have become increasingly concerned about the impact of IH on patients and their family life. During consultation, parents often express their concern about the visible lesion of their child. In some cases several psychosocial problems may occur for the patients and their children, particularly above the age of 4-5 years, when the child goes to school. From this age, IH patients start to experience themselves as being different.[73] These facts play also an increasingly important role in both the attitude of physicians treating children with an IH and their decision whether or not, and when to start treatment.

1.3 Management and treatment

In 2008, a Dutch treatment guideline, initiated by parents and patient support group Hevas has been published and an update will appear in the immediate future, with the addition of beta-blockers as therapeutic modality. Despite the relatively high frequency of IH and the potential severity of complications, there are however no international uniform guidelines for treatment. Nevertheless, in the last decades, several modalities in the treatment of IH have been described. Some of them are rarely or no longer used (radiation therapy, cryotherapy, imiquimod and bleomycin) related to disappointing efficacy and/or side effects. Prospective data concerning the efficacy and safety of treatment modalities for IH have not yet been generated. Available data are confounded by the lack of consensus on treatment criteria and objective outcome measurements. The most common management and treatment modalities for cutaneous IHs will be described in the paragraphs below.

1.3.1 'Active non-intervention'

In a vast majority of IH patients, the best approach is choosing not to treat. This is a valuable choice for children with small innocuous IHs where parental concern may be much greater than the actual threat of the condition. A proactive approach of the physician and attention for the coping of the parents is of great importance in these cases. At the initial visit there should be a clear explanation of the natural history and the general prognosis, for example illustrated with photographs. Also the advantages and disadvantages of the various treatment options should be discussed. Parents should be provided with reputable sites/resources that can help in supporting families with an IH patient. Regular visits particularly during the proliferation phase, with assessments and serial photographs to document growth velocity are also recommended. This strategy called 'active non-intervention' is the most optimal approach for the majority of patients.

1.3.2 Corticosteroids: topical, intralesional and systemic

There are reports on the beneficial effect of potent topical steroids (particular clobetasol propionate) on small superficial IHs, particularly early in the proliferation phase. However, randomized controlled trials, to support the use of topical corticosteroids in the treatment of IH are lacking in literature. Potential side effects of topical corticosteroids include: systemic absorption, cutaneous atrophy and striae, making close follow-up necessary.

Intralesional corticosteroids were initially used for periorbital IHs by ophthalmologists, but the risk of retinal artery damage and blindness has ensured that intralesional corticosteroid treatment for these IHs is no longer applied.[74,75] Intralesional steroids for IH on other sites (e.g. nasal tip, lip) can be effective in stabilizing growth or decreasing the size of the IH, particularly in the proliferation phase. Intralesional application may be effective in small tumors, where the medication is likely to be distributed equally. Mostly, triamcinolon 10 mg/ml is used and doses do not exceed 1-2 mg/kg per injection. The injections can be repeated at six-week intervals and usually one to three injections are required and anesthesia is not obligatory. Possible side effects include bleeding, skin atrophy, infection and adrenal suppression.[67]

Systemic corticosteroids (prednisolone, prednisone) were first described in 1960 in the treatment of IH and were until recently, the mainstay of therapy.[76] Prednisolone, administered at 2-3 mg/kg/day, in a single daily dose, is reported in several studies as an effective therapy for the majority of the IH patients, predominantly in the proliferation phase, as defined by cessation of growth or involution.[77-79] Several side effects are however reported, particularly in case of long-term treatment: gastro-intestinal upset and irritability, weight gain, Cushingoid appearance, hypertrophic cardiomyopathy (HCM), hypertension, delayed growth, adrenal suppression and immunosuppression.[80] Catch-up growth occurs in most cases, nevertheless numerous courses of corticosteroid therapy, can lead to serious long-term side effects.[81] The careful monitoring of patients treated with oral corticosteroids is therefore emphasized in literature.

1.3.3 Laser-therapy

Pulsed dye laser (PDL) is the most commonly applied modality for superficial IHs, ulcerated IHs and residual lesions, with minimal requirements for anesthesia. Because PDL has only a limited penetration depth, it is not used for IHs with a deep compartment. The risks of scarring and induction of ulceration are actually limited because of the current use of epidermal cooling systems and longer pulse duration.[82,83] As opposed to the layman's ideas, it is important to realize that laser treatment of the tiny initial IH, never prevents the development of any bulky IH.[84]

Lasers with longer wavelength like Nd:YAG may be used in difficult, recalcitrant cases, but implicate a greater risk of scarring.[85]

Fractionate CO2 laser is reserved for the resurfacing of involuted lesions, to diminish textural changes.[86] Sometimes laser treatment is used successfully, in combination with other particularly systemic therapies.[46,87]

1.3.4 Interferon

Since 1989, several studies reported the use of subcutaneous interferon alpha-2a and -2b in the treatment of IH. Interferon has anti-angiogenetic properties, it stops the growth of IH slowly and may result in a higher rate of actual shrinkage than seen with corticosteroids. Subsequently, reports appeared of serious side effects including spastic diplegia in up to 20% of patients.[88] Given the severity of this potential complication, the use of interferon in the treatment of complicated IH is limited.

1.3.5 Vincristine

Vincristine is a vinca alkaloid widely used in cancer chemotherapy and successful in treating IH, most commonly in conjunction with other therapies.[89] It is administered intravenously at a dose of 1.0-1.5 mg/m^2 weekly. This modality also has limited use due to the need for central line access for chronic administration as well as the potential severe side effect of peripheral mixed sensory-motor neurotoxicity.[46] It is only indicated for severely threatening IHs, resistant to other therapies.

1.3.6 Surgery

In some cases, surgical excision may be the best therapeutic choice. Particularly in case of large pedunculated IHs that are located where a surgical scar will be less noticeable. The expected cosmetically aspect of the scar needs to be weighed against the expected residual lesion after involution of the IH. In some instances, eventual surgical involvement is inevitable because of permanent fibrofatty tissue. Besides, the timing of surgical intervention is often a difficult decision. The clinician should consider whether postponing the operation, allowing further natural involution, may eventually result in a smaller size of the operated lesion with finally a smaller scar.[16,46] On the other hand, choosing to operate before the school-going age in a lesion that eventually may need surgery after all, may also be an option as the IH is (significantly) decreased and the intervention 'forgotten' by the young child.

1.3.7 Propranolol

1.3.7.1 Propranolol and IH

The effectiveness of propranolol in the treatment of IH was serendipitously discovered by Léauté-Labrèze et al. in 2008. In two children their IH showed very rapid involution when treated with propranolol, which was given for other indications. The first child received propranolol for obstructive HCM, secondary to corticosteroids given for a nasal IH. The second child was initiated on propranolol for increased cardiac output due to a large, bulky IH in the head and neck region.[90] Since this initial report, there has been an outbreak of case reports and case series in medical literature describing efficacy and potential side effects of propranolol for IH. From the current clinical experience, propranolol has shown to be rapidly effective for IH and well tolerated. It seems that propranolol stops the growth

and induces regression of IH much better than previous therapies. These observations have led to rapid and worldwide implementation of this new therapeutic modality for IH.[91]

1.3.7.2 Mechanisms of action

Propranolol is a synthetic, highly lipophilic, beta-adrenergic receptor-blocking agent that is classified as non-selective because is blocks both beta-1 and beta-2 adrenergic receptors. This beta-blocker is a pure antagonist without partial agonistic effects. Propranolol has been used for decades in pediatric patients, primarily for the prevention and treatment of cardiac arrhythmias, HCM, hypertension and to prevent cyanotic spells in Tetralogy of Fallot. The standard dosing is 0.5-4.0 mg/kg/day, however much higher dosages are given to reduce the risk of sudden cardiac death in HCM.[92] Its antihypertensive effects result from decreased heart rate, decreased cardiac contractility, inhibition of renin release by the kidneys and decreased sympathetic tonus. Control of IH-growth by propranolol is hypothesized to work via different mechanisms with distinct early, intermediate and long-term effects, which can be attributed to different pharmacological targets.

a. Vasoconstriction - early effect

Propranolol inhibits epinephrine-mediated vasodilatation, leading to vasoconstriction of the microvessels of the IH, resulting in rapid color change and tissue softening. These effects can be observed within 1-3 days after the onset of therapy.[90,93]

b. Inhibition of angiogenesis - intermediate effect

Beta-adrenergic receptors are G-protein-coupled receptors, which, when activated by adrenergic catecholamines, can promote a series of intracellular signal transduction pathways including that of angiogenetic factors such as VEGF or bFGF and some matrix metalloproteinases (MMP) such as MMP-2 and MMP-9, involved in degradation and transformation of extracellular matrix proteins. These signal transduction pathways are inhibited by beta-blockers, resulting in a reduction of angiogenesis.[93]

c. Apoptosis - long-term effect

Blockade of beta-adrenergic receptors by propranolol can induce apoptosis of different cell types in vitro, e.g. endothelial cells or pancreas carcinoma cells. It is hypothesized that beta-adrenergic antagonists are capable of disengaging the inhibition of apoptosis caused by beta-adrenergic agonists, resulting in an increased apoptosis rate.[93]

d. Renin-angiotensin system

More recently a fourth mechanism has been suggested after the discovery of the presence of both angiotensin-converting enzyme (ACE) and angiotensin II-receptor on the CD34+

endothelial progenitor cells of the microvessels of proliferating IHs. This, together with the observation of increased renin levels in premature, female and Caucasian infants, the prototypical IH patient characteristics, has resulted in the investigation of the position of the renin-angiotensin system (RAS) in the pathogenesis of IH. Propranolol reduces renin activity in the periphery by reducing plasma renin activity, resulting in reduced angiotensin I (AT I) and eventually AT II levels. A reduction in AT II levels causes a reduction in proliferation of the hemogenic endothelium of proliferating IHs combined with an increased rate of cellular apoptosis through the tumor necrosis factor (TNF)-related apoptosis ligand pathway. The natural history of IH is consistent with the reduction in renin levels that occur physiologically after the first year of life. Also the effect of beta-blockade on IH is in line with the interfered mechanism of action of propranolol through the RAS.[94,95]

1.3.7.3 Adverse events

Beta-blockers have a well-documented safety and side effect profile. A review of literature of the 40 years of clinical use at therapeutic doses in children younger than 7 years of age, revealed no cases of mortality or serious cardiovascular events, except for one girl, in relation to an overdose.[96,97] The most frequently reported serious complications after use for IH are hypotension, pulmonary symptoms, related to direct blockade of adrenergic bronchodilatation, hypoglycemia, asymptomatic bradycardia and hyperkalemia. The most commonly reported, non-potentially life-threatening complications were sleep disturbances including nightmares, somnolence, cold extremities and gastro-esophageal complaints.[91]

Hypoglycemia is considered the most serious side effect of propranolol. Propranolol may cause hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis and lipolysis. Young children are more susceptible to hypoglycemia for two reasons. Firstly, their lower glycogen stores lead to reduced fasting ability and secondly their glucose utilization rates are higher when fasting. Children previously or actually treated with oral corticosteroids, are more at risk due to adrenal suppression.[98] Another concern is the masking of early sympathetic signs of hypoglycemia such as tachycardia, sweating and palpitations by propranolol. It is therefore advised that propranolol should be temporarily discontinued in case of (preoperative) fasting or intercurrent illness, associated with diarrhea and vomiting.[99]

1.4 Aims and outline of the thesis

1.4.1 Aims of the thesis

The studies carried out in this thesis are designed to investigate the implications of the changing landscape of treatment of complicated IHs since the discovery of propranolol as treatment modality. Secondary, we intend to achieve more insight in complicated IHs.

The following aims are formulated:

Aim 1: To explore the indication area and treatment regimen of propranolol in infantile hemangioma.

Aim 2: To get more insight in the role of propranolol in the treatment of ulceration, the most common complication of infantile hemangioma.

Aim 3: To enlarge knowledge about quality of life aspects in patients with infantile hemangioma and their families, especially with respect to different treatment modalities.

Aim 4: To explore the future role of quantitative imaging analysis, in particular 3D stereo-photogrammetry in the follow-up of infantile hemangioma growth and regression.

Aim 5: To investigate and describe the broader applicability of propranolol in vascular tumors.

1.4.2 Outline of the thesis

In ***Chapter 2,*** a prospective study is described of the first 174 patients treated with propranolol for complicated IHs. The experiences of the Hecovan-working group are delineated with the focus on the indications area and treatment regimen.

The first part of ***Chapter 3***, comprises a retrospective analysis, investigating the differences between ulcerated and non-ulcerated IHs. These characteristics could be important in the consideration of whether or not to start treatment. In the second part of chapter 3, the results of a retrospective study are reported, in which twenty patients with an ulcerated IH treated with propranolol were compared with a historical control group. In this study the role of propranolol for patients with ulcerated IH is explored.

Chapter 4 presents a retrospective study exploring the impact of treatment and contentment with treatment-outcome for propranolol-treated IH patients and their parents compared with a matched patient group treated with oral corticosteroids.

In ***Chapter 5***, a pilot study is described, in which the role of two methods in 3D stereophotogrammetry for the measurement of volume changes in facial IH is explored.

In the first part of ***Chapter 6***, the role of propranolol for airway IHs is described based on a case series of five patients and a review of the experiences in literature. In the second part of chapter 6, a patient with Kaposiform hemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP) is described, treated with propranolol and only a total of 4 weekly doses vincristine.

In ***Chapter 7***, the aims of this thesis are discussed in the view of our findings described in chapter 2-6. Moreover, recommendations for additional clinical research are outlined and viewpoints for future developments are revealed.

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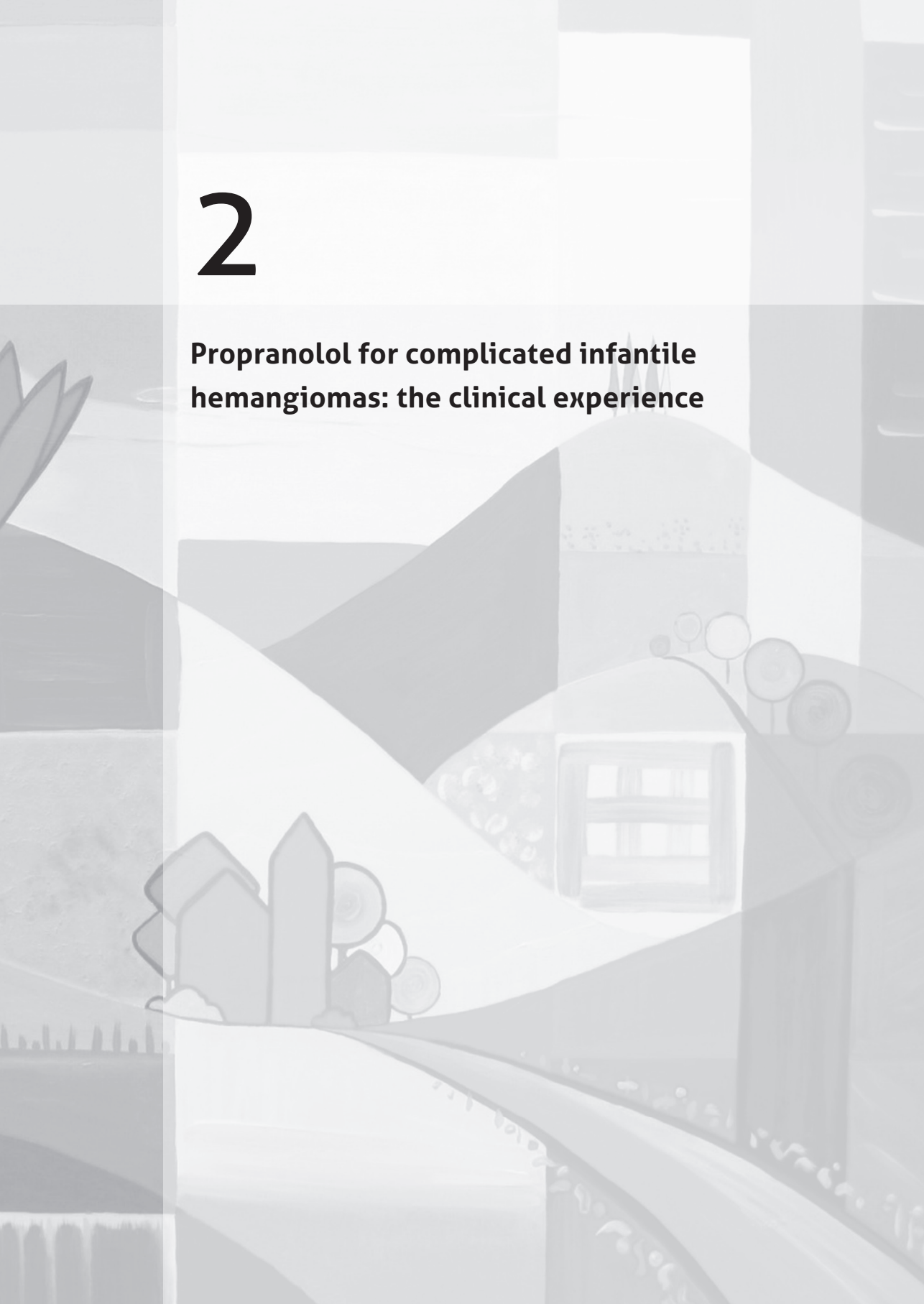
2

Propranolol for complicated infantile hemangiomas: the clinical experience



2.1

Propranolol in a case series of 174 patients with complicated infantile hemangioma: indications, safety and future directions

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Summary

Background Infantile hemangioma (IH) is a benign, common and self-limiting tumor of infancy; only a minority of cases need active treatment. Currently, propranolol appears superior to classic treatments.
Objectives To document in a prospective study indications and side effects of propranolol for complicated IH in a large patient group.
Methods Analysis of prospectively collected data was performed on 174 patients with IH treated with propranolol in a tertiary referral centre from September 2008 to January 2012.
Results The group consisted of children with a potentially threatening and/or complicated IH; the girl/boy ratio was 123/51, and the mean age at the start of treatment was 4.8 months. In 173 cases (99.4%), treatment was successful, as assessed non-quantitatively by clinical observation. This striking effect was characterized by immediate cessation of growth, softening, fading of the erythema and rapid induction of regression. The mean duration of treatment was 10.7 months. The most important adverse effects were hypotension (3.4%), wheezing (9.2%), nocturnal restlessness (22.4%) and cold extremities (36.2%). In one patient, propranolol was stopped. In 15 patients it was necessary to reduce the dose, although the lower dose was still effective.
Conclusions In this study, propranolol was effective and safe in almost all patients with complex IH. Administration of systemic medication to an infant with a benign condition requires careful consideration, as only a minority of patients with IH require an active medical intervention. A shift of the indication of propranolol for IH is evident, expanding its application for life-threatening situations or severe functional impairment to early prevention of disfigurement or cosmetically permanent sequelae. However, the indication for such an active approach should be determined by experienced physicians.

Infantile hemangioma (IH) is the most common tumor of childhood, with an estimated prevalence of 10–12% in populations of European descent. IH is characterized by an inconspicuous appearance at birth, a proliferative phase throughout the first year of life with disproportionate growth, followed by a slow involution phase that lasts on average until the age of 7–10 years. Residual lesions are frequent and depend on the degree of epidermal involvement.[1] This benign course of IH in general justifies a conservative approach during the growth phase of the tumor. Nevertheless, 10% of all cases of IH cause substantial morbidity, which is an indication for an active approach in the proliferation phase.[2] Until recently, the first-choice treatment in this patient group consisted of administration of high-dose oral corticosteroids.[3] In June 2008, Léauté-Labrèze et al.[2,4] serendipitously observed the extraordinary and fast effect of the adrenergic beta-antagonist propranolol on IH. This observation has caused a worldwide shift in the therapeutic approach for complicated IH. Our tertiary referral centre also started with propranolol treatment in patients with a complicated IH.

The experience with 174 children is presented as 'real clinical practice' data in the current report and is the largest group in the literature to date.

Materials and methods

Treatment protocol

After the treatment indication for propranolol was established by a multidisciplinary team, the pediatric cardiologist monitored (initiation of) propranolol treatment in all the patients. Prior to treatment, a medical history was taken and patients were examined physically. An echocardiogram (ECG) was performed in all patients and echocardiography was performed in our first 75 propranolol patients. However, with our growing experience, echocardiography was performed only in a subset of patients. These included children with signs of a syndromal IH associated with cardiac pathology, such as PHACES (posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome),[5] cardiac murmur, ECG abnormalities, or signs of cardiac failure and in children with a large bulky IH.

Propranolol was administered orally; the starting dosage was 0.7–1.0 mg kg^{-1} daily in three divided doses. The dose was gradually increased to the total target dosage of 2.0–2.5 mg kg^{-1} daily. Initially, treatment was started clinically for all infants. However, in a later stage, with our increasing experience, treatment was started at home in patients without contraindications. The initial low dosage was given at home, followed by monitoring in a day care setting while increasing the dosage to 2.0–2.5 mg kg^{-1} daily.

Heart rate and blood pressure were measured three times a day during the first 3 days if treatment was started in a clinical setting. If treatment was given in day care, heart rate and blood pressure were measured after dose increment, three times in about 8 h. In the

case of young premature infants and neonates with a higher risk for hypoglycemia, renal dysfunction, cardiac morbidity and hypotension, a lower dosage of 1–1.5 mg kg^{-1} daily was given, which was gradually increased to the target dosage. For infants aged < 3 months, a fasting glucose level was determined. In addition, the parents of all patients were informed extensively about the increased risk and characteristics of hypoglycemia. In cases of a threatening IH resulting in, for example, compromised airway function, the target dosage was adjusted upwards to a maximum of 3.0 mg kg^{-1} daily. All patients with a periorbital IH were also monitored by an ophthalmologist and orthoptist during treatment.

The follow-up interval was every 6 weeks in the first 6 months of treatment; subsequently this interval was extended to 3 months. The propranolol dose was adjusted to the target dosage of 2–3 mg kg^{-1} daily, guided by body weight, until the age of 9 months, after which the dose was no longer increased. For patients in whom an additional effect was necessary, dose adjustments were made above the age of 9 months. The degree of improvement (fading and softening) was recorded by two observers during each visit (D.J.J.H., C.J.M.v.d.V.). Possible adverse events were recorded.

Treatment was continued during the proliferation phase and gradually tapered in 2–3 weeks. In general, the reduction schedule was as follows: 2 weeks of two divided daily doses, 1 week of one daily dose. Treatment was stopped at the age of 12–18 months, depending on the localization of the IH and/or primary treatment indication.

Analysis

Data obtained from patient files of all the 174 patients with IH treated with propranolol between September 2008 and January 2012 were analyzed to define the characteristics of the study group. The numeric data are reported as mean (SEM).

Results

General characteristics

In total 174 patients were treated with propranolol; 123 were girls (70.7%). Thirty-nine patients (22.4%) were born prematurely; 10 were extremely premature (gestation < 32 weeks). The patients had on average 2.4 IHs (SEM 0.3). Further characteristics of the treated IHs are listed in Table 1.

Treatment was indicated in potentially threatening and/or complicated IHs. The primary treatment indications of the IHs are shown in Table 2.

For 168 of the 174 patients (96.6%), treatment with propranolol was successful within 72 h. In five patients (2.9%) the effect was visible within 2–3 weeks. Improvement was characterized by fading and softening of the IH. The effect of propranolol is illustrated in three infants with a complicated IH, all with different treatment indications (Figures 1–3). The five patients with airway obstruction involving the upper respiratory tract due to an IH improved within hours, thereby reducing or preventing an intensive care stay.

Table 1 Characteristics of infantile hemangioma (IH) (n = 174)

Characteristic	n[a]	%
Growth pattern		
Superficial macular	14	8.0
Superficial nodular	73	42.0
Deep	30	17.2
Mixed	57	32.8
Localization		
Head /neck	141	81.0
Eyelids / periorbital	65	
Nose /perinasal	19	
Lips /perioral	18	
Subglottic	3	
Ear /periauricular	7	
Cheek	8	
Beard area	2	
Neck	4	
Scalp	9	
Forehead	6	
Trunk	4	2.3
Extremities	11	6.3
Diaper area	18	10.3
Total number of ulcerated IH	60	34.5

[a] Number of IHs with the primary treatment indication.

Besides treatment with propranolol, in two out of five patients with an airway IH oral corticosteroids were administered because of initial unclear diagnosis. After the diagnosis of IH was established, propranolol was started successfully and corticosteroids were reduced. For ulcerated IHs, in some patients, propranolol was initiated right away. In other patients, treatment was started with oral antibiotics combined with non-adhesive silicone or foam dressings and low-threshold pain medication. Propranolol was started when the above treatment regimen had insufficient effect. In 27 of the patients (45%) with an ulcerated IH, oral antibiotic treatment had been started before treatment with propranolol was initiated.

In patients with a periorbital IH, no major ophthalmological complications, such as amblyopia, have been seen to date, except for two patients who started propranolol relatively late, at the ages of 7.1 and 14.0 months.

Table 2 Treatment indications

Indication	*n*	%
(Impending) visual impairment	69	39.7
(Impending) nasal obstruction	11	6.3
(Impending) hearing impairment	5	2.9
Cosmetic risk / face deformity[a]	14	8.0
Ulceration (primary treatment indication)	49	28.2
Ulceration risk in near future	7	4.0
Bleeding	3	1.7
Airway obstruction /stridor	5	2.9
Nutritional problems	7	4.0
Mechanical impairment[b]	4	2.3
Total	174	100

[a] Cosmetic risk /facial deformity: (facial) infantile hemangioma (IH) with very high / great risk of psychosocial implications now and in the future. [b] Mechanical impairment: when size or location of the IH created a restriction in daily functioning.

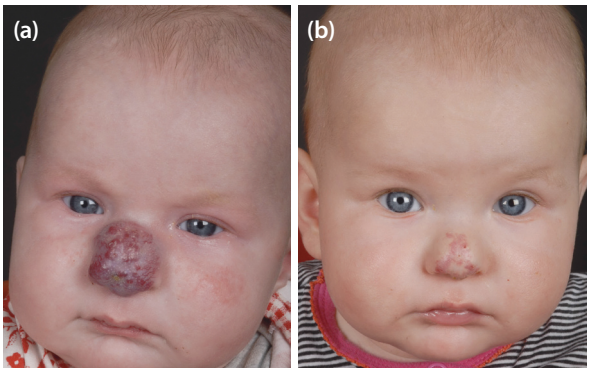

Figure 1
(a) A 3-month-old girl with hemangioma of the nose with painful ulceration and obstruction of nostrils at the start of treatment with propranolol; **(b)** the same girl at the age of 8 months after propranolol treatment.

Treatment regimen

At the time of analysis, 113 patients (64.9%) had completed their treatment. The mean age at the start of the treatment was 4.8 months (SEM 0.2, range 0.9–29.0 months). Mean duration of treatment was 10.7 months (SEM 0.4).

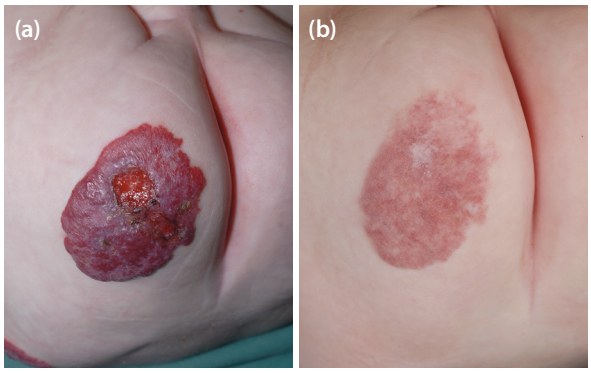

Figure 2
(a) A 3.5-month-old boy with an ulcerated hemangioma of the buttock; **(b)** the same boy at the age of 6.5 months after propranolol treatment.

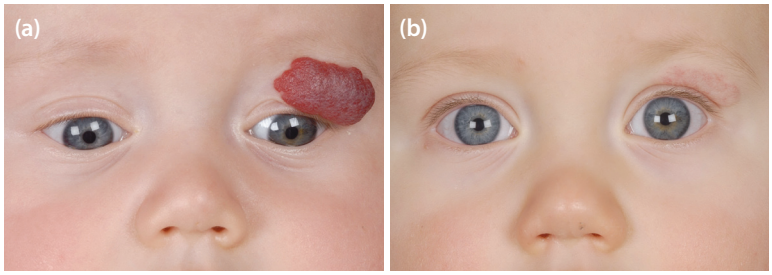

Figure 3
(a) A 4.5-month-old boy with hemangioma affecting the upper eyelid; **(b)** the same boy at the age of 11.5 months after propranolol treatment.

After discontinuation of propranolol treatment, 14 of 113 patients (12.4%) had reappearance of some swelling, in 11 patients (9.7%) an increase in erythema appeared, and in nine patients (8.0%) both changes were seen. In one patient there was a slight increase in blue color and in one patient mild ulceration appeared after cessation of treatment, characterized by rapid improvement. The rebound swelling of the IH was significant enough to merit a second course of propranolol in four patients: two patients with eyelid IHs, one patient with a large facial IH with respiratory implications and one patient with a nasal IH. The second course of propranolol lasted on average 7.9 months (range 2.0–12.0 months) and was successful in all patients. In these four patients, the first course of propranolol had been stopped beyond the proliferation phase. For three patients rebound swelling during the reduction phase was the reason to slow down the tapering of propranolol, with good results.

Table 3 Possible side-effects during treatment in 62.1% (108) of the 174 patients

	n	%
Effects on blood pressure	6	3.4
Nocturnal restlessness	39	22.4
Cold extremities	63	36.2
Respiratory symptoms	16	9.2
Medication necessary	*9*	
No medication necessary	*7*	
Less active during the day /sleepy /drowsy	28	16.1
More active /restless in the daytime	9	5.2
Gastrointestinal complaints	12	6.9
Feeding difficulty	3	1.7
Onset of /worsening of ulceration	4	2.3
Breath-holding spells	2	1.1

In general, a target dosage of 2–2.5 mg kg^{-1} daily was adequate. For 16 of the 174 patients (9.2%) a lower starting dosage of propranolol was chosen than the median target dosage of 2–2.5 mg kg^{-1} daily, ranging from 0.75 to 1.9 mg kg^{-1} daily (mean 1.5 mg kg^{-1} daily) because of (extreme) prematurity, young age, comorbidity or low blood pressure at the starting dose. For 15 patients (8.6%), the dose was adjusted downwards during treatment due to adverse events, in particular respiratory symptoms, effects on blood pressure and nocturnal restlessness. The lesions continued to respond well, without adverse effects, despite dose reduction. In three patients with the indication of airway obstruction (n = 2) and repeated severe bleeding (n = 1), a higher target dosage of 3 mg kg^{-1} daily was chosen. For two patients the dosage was successfully adjusted upwards to 3 mg kg^{-1} daily during treatment because of the need for an additional effect given the relatively slow initial effect of the propranolol. In one patient with extreme nocturnal restlessness, a switch was made to the selective adrenergic beta-antagonist atenolol 1 mg kg^{-1} daily in two divided doses, resulting in comparable clinical efficacy and improvement of the sleep pattern.

Safety

During follow-up visits, all possible side effects were recorded as shown in Table 3. Possible side effects during treatment were recorded for 108 patients (62.1%). Despite this relatively large number, the adverse reactions were in general not serious and were reversible and dose dependent. Lowered blood pressure was noted in six patients. In five of these patients, blood pressure effects were observed in the first 3 days of clinical treatment. For the sixth patient, possible anamnestic hypotension at home was reported but could not

be verified with certainty. This did not require further follow-up. Sixteen patients developed respiratory problems during treatment, characterized by wheezing during upper respiratory tract infections. In nine of these patients, treatment was started with inhaled corticosteroids, inhaled sympathomimetics or both. In one of the first patients treated in our centre, an extremely premature infant (30 weeks' gestation) with a periorbital IH, the therapy had to be discontinued early due to hypotension, drowsiness and cold extremities at a dosage of 1.0 mg kg^{-1} daily. Treatment was continued with corticosteroids. This case was one of the first children treated with propranolol in our centre. In retrospect, further reduction of the dosage might have been tolerated and effective. In all other patients with decreased blood pressure due to propranolol, treatment was successfully continued after a dosage reduction.

For 15 of 113 patients (13.3%), the parents reported that their child became more active after discontinuation of treatment.

Discussion

Based on the currently available data, propranolol appears to be more successful for the treatment of IH than any other treatment modality, with a possible exception of surgery in selected cases.[6] It is anticipated that this will be progressively demonstrated in emerging randomized controlled trials, one of which has been published with promising outcomes.[7]

Propranolol is a highly lipophilic nonselective beta-adrenergic antagonist with an inhibitory effect on both β1- and β2-adrenoceptors with similar affinity. Its main effect in IH can be explained by different mechanisms: vasoconstriction; inhibition of angiogenesis by downregulation of angiogenic factors, vascular endothelial growth factor and basic fibroblast growth factor; and induction of apoptosis of capillary endothelial cells. These mechanisms correspond, respectively, with the following clinical observations: softening and fading, cessation of growth, and long-term regression.[8]

As IHs have variable localization, size and type, it is almost impossible to describe the treatment effect in a standardized manner. Therefore, in this study a treatment was considered successful if obvious improvement was seen in color and size, as evaluated subjectively by two observers. In 173 of the cases (99.4%) propranolol treatment was successful; fading and softening of the IH was seen, usually starting within 72 h after the start of treatment. Growth of the IH stopped in all cases and regression was judged as significant at the end of treatment (9–18 months).

Like many drugs used in children, there are no pharmacokinetic data and no prospective controlled studies that can be used to make an adequate treatment regimen and follow-up scheme for this patient group. At the current time, a target dosage of 2–3 mg kg^{-1} daily, with regular adaption to the body weight, is considered a safe and effective dosage for the healthy infant.[2,9,10] However, in the recent literature a minimal dosage

required to induce involution of 1.5–2.0 mg kg^{-1} daily has been described.[11] This was also the case for several patients in this study. The target dosage could be adjusted downwards successfully during initiation or during the course of the treatment, which appears to indicate that for certain patients lower dosages may also be effective. Large-scale studies are required to establish the optimal dosage. In some cases, especially in patients with IH with airway involvement, higher dosages (3 mg kg^{-1} daily) and strict dose adjustments were necessary, because the effect of propranolol on stridor diminished at the moment that the relative dose decreased due to the weight gain of the child.

Treatment duration was adjusted for the type of IH and the specific treatment indication. In deep and mixed IHs the proliferation phase starts and stops later, treatment was therefore continued until the age of 12–16 months. In cases of ulceration, for example, treatment was continued to 9–12 months of age, because of the marginal risk of recurrence of ulceration after this phase. Deep periorbital IHs and airway IHs, on the other hand, required treatment up to 15–18 months of age, because of the potential life-threatening implications of swelling after cessation of treatment.

Rebound swelling in this study was generally not interpreted as regrowth but as swelling that occurred due to decreased vasoconstriction after stopping propranolol. This refill seems to occur particularly in more bulky IHs, which exhibit a sponge-like residual lesion.

At the end of the treatment period, a slow reduction of the dose in 2 or 3 weeks is indicated, as abrupt discontinuation of beta-blockers bears the risk of cardiac hyper-reactivity due to upregulation of beta-receptors.[12]

Propranolol has been used for more than 40 years in young children aged < 7 years, particularly for cardiological indications, without severe cardiovascular events or lethal outcome.[13] Adrenergic beta-antagonists have a well-documented safety and side-effect profile. The main side effects of propranolol are bradycardia, hypotension and hypoglycemia. In addition, bronchospasm, rash, gastrointestinal symptoms, fatigue, behavioral changes, peripheral vasoconstriction and sleep disturbances have also been described. The most serious side effect of propranolol is hypoglycemia, also reported following its use for IHs, either aggravated or not by the fact that propranolol can mask early clinical symptoms of hypoglycaemia.[14–16] The patient groups with higher risks for hypoglycemia are patients aged < 3 months with decreased food intake or concomitant treatment with oral corticosteroids, in particular in a reduction schedule. In these patient categories, intensive and frequent monitoring is therefore recommended as well as good instructions for parents.[12,17] In our patient group, the measured fasting glucose levels were normal and fortunately no hypoglycemic side effects were seen. Additionally, propranolol diminishes cardiac performance and can mask the clinical signs of cardiac failure. This means that special care must be taken in patients with cardiac comorbidity, particularly in patients with cardiac failure, due to a large, bulky IH.

With our increasing experience with propranolol, in selected cases we chose to start the lowest dose at home and to increase to the target dosage during day care. This protocol was followed in patients born at term, with normal birth weight and no abnormalities on physical examination or ECG. In all other cases, treatment was started in hospital. Complication rates were similar for in- and outpatients. Important advantages of the outpatient start are the quick and easy application of the treatment without any time delay due to limited clinical capacity, and the fact that it is more cost-effective and patient friendly. The main disadvantage of outpatient initiation of propranolol treatment is the absence of monitoring of blood pressure and heart rate during the first doses. This is why this protocol was applied only to a minority of children; initiation of propranolol in a clinical setting is still our preference.

Following the observation of Léauté-Labrèze et al.,[4] several case series have been described in which a large variety of clinically different IHs were treated successfully with propranolol.

Initially, predominantly complicated IHs were treated. The indications are gradually broadening and are starting to include cosmetically disturbing cases such as large facial IHs. For both indications (functional and cosmetic), early initiation of treatment is probably the best, before rapid expansion of the tumor. If the IH is located mainly in important cosmetic areas, an early start with propranolol treatment may reduce the residual lesions after involution, making cosmetic correction less complicated or even unnecessary.[1,18] To date, there is no evidence that early propranolol treatment leads to less disturbing residual lesions. However, for ulcerated IHs an early start appeared to result in shorter ulceration time; an analogy with less severe residual lesions due to an early start seems likely. Future research will determine the appropriate cosmetic indications. This shift in indications makes timely assessment by an experienced physician necessary.[19–21]

In accordance with recent literature, we also noted a positive effect on the rate of involution in the few cases where propranolol was started at the end of the growth phase or thereafter.[22,23] However, the residual lesions (e.g. fibrofatty tissue, skin surplus) are expected to be comparable with the situation in which treatment was not administered.

Besides treatment modifications pertaining to initiation and/or duration, future developments may include the use of more selective beta-blockers. Reports on selective beta-blockers, such as atenolol or acebutolol, have already been published, but further investigation is required as to whether this selectivity is accompanied by a more favorable safety–efficacy profile.[24,25]

Alternative approaches, such as the possible beneficial effect of angiotensin-converting enzyme (ACE)-inhibitors, will be further explored in the future. The renin–angiotensin system has recently been determined as a factor in the pathogenesis of IH. Expression of ACE and angiotensin II receptor-2 on immature capillaries of a proliferating IH has been observed and it has been proposed that beta-blockers decrease renin activity, resulting in decreased angiotensin II in IH tissue, leading to accelerated involution.[26] The ACE-inhibitor captopril was recently reported to be effective.[27,28]

There is currently limited experience with the application of topical beta-blockers such as timolol. A beneficial effect can be seen, especially in superficial IHs, but the topical approach seems insufficient for the expansive growth of bulky deep IHs. On the other hand, application of topical beta-blockers in very young children (aged < 4 weeks) with a still flat IH appears to be a therapeutic option.[29] However, topical beta-blockers must be prescribed with caution, especially in larger lesions, because of the risk of systemic absorption and subsequent side effects.[30]

In conclusion, propranolol is definitively a valuable and promising therapeutic option for IH. In our patient group it was effective and safe in almost all patients. However, for some patients dose adjustments were necessary because of side effects. Future research is required on the treatment regimen and long-term follow-up. From the extensive experience of our tertiary referral centre and data from the literature, we expect that in the near future propranolol will become the first-choice treatment in complicated and disfiguring IHs, and very likely with further expanding areas of indication. On the other hand, it is important to emphasize that giving beta-blockers to young infants has to be justified for each individual patient as IHs are common, benign, self-limiting tumors that usually do not need an active approach. Only a small minority of IHs are life- or function-threatening, and require therapy. Large, facial IHs with serious cosmetic outcomes may also be eligible for an active approach. Therefore, patients with life-threatening lesions or lesions with a severe psychosocial impact should be assessed individually and early by an experienced physician or a dedicated multidisciplinary team. The characteristics of the IH and the patient and the potential risk of propranolol treatment need to be taken into account.

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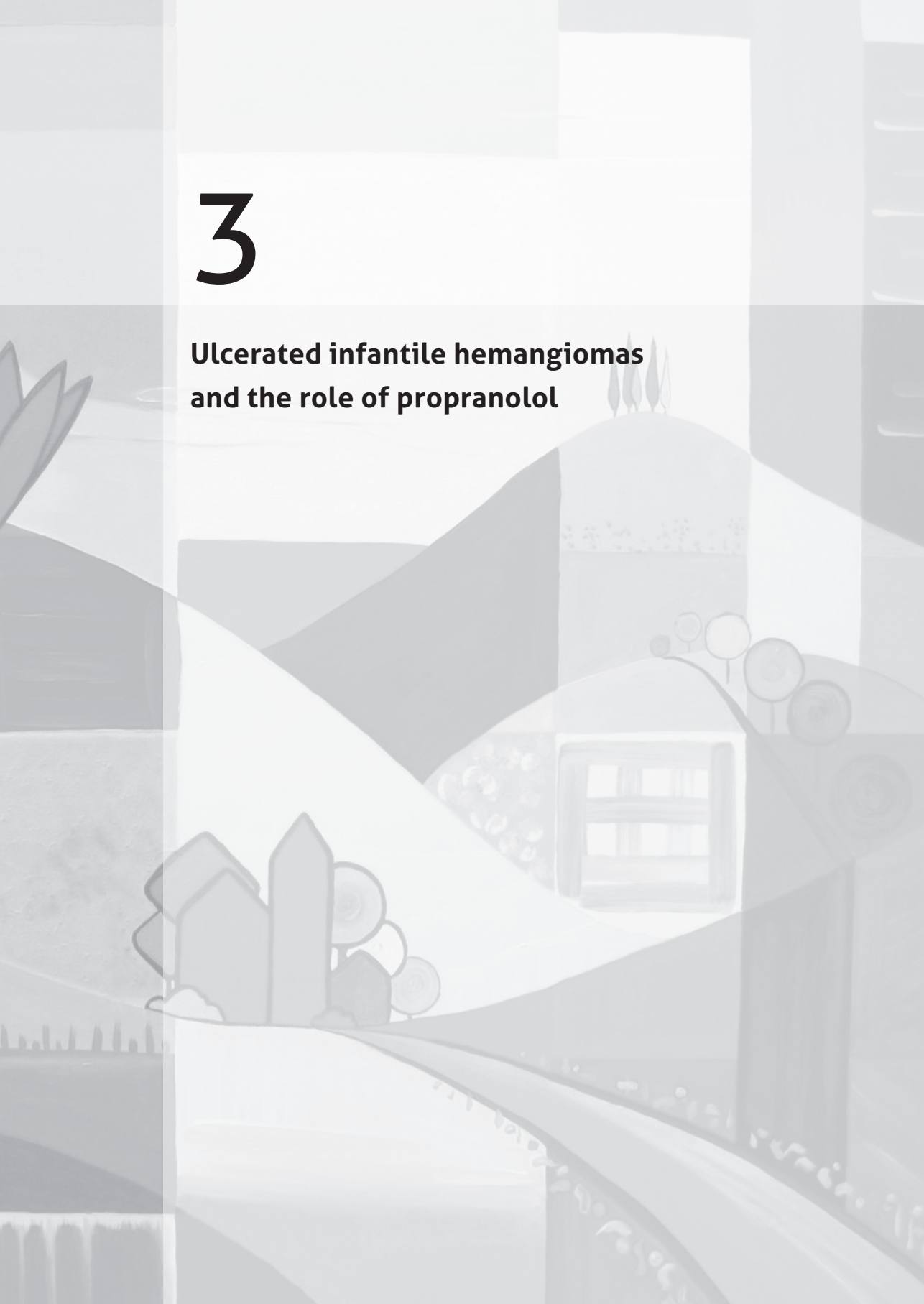
3

Ulcerated infantile hemangiomas and the role of propranolol



3.1

Differences between ulcerated and non-ulcerated hemangiomas, a retrospective study of 465 cases

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Summary

Our purpose was to get better insight into the ulceration of hemangiomas, by comparing patient characteristics of non-ulcerated hemangiomas with hemangiomas with active or past ulceration. A retrospective analysis was performed of files of patients who visited the Radboud University Medical Centre Nijmegen (UMCN), the Netherlands, between 1997 and 2007 for one or more infantile hemangiomas. The medical records of 465 patients were reviewed. Twenty three percent of the patients were diagnosed with ulceration. The size of ulcerated hemangiomas was significantly larger (28.6 cm^2 *vs.* 6.0 cm^2, $p < 0.05$). Predilection areas for ulceration were the head and neck region and the anogenital region. Ulceration was significantly most frequently seen in hemangiomas with a superficial (epidermal) component (98.5%, $p < 0.05$) and a segmental distribution (29.3%, $p < 0.05$). Ulceration most frequently took place during the proliferation phase of the hemangioma (83.1%). In the whole study population the male to female ratio was 1:2 compared to a tendency to more girls (1:3) for the group with ulcerated hemangiomas ($p = 0.08$). We conclude that larger, more superficial hemangiomas in areas more susceptible to trauma and contamination were more likely to ulcerate. This study contributes to the possibility of assessing the likelihood of ulceration in an individual patient.

Although infantile hemangiomas (IH) occur in 10-12% of children younger than 1 year of age, this benign tumor is not well understood. One of these unknown areas is ulceration.[1] Although ulceration is the most common and distressing complication of IH, possibly affecting between 5% and 13% of the IH, little is known about its pathogenesis.[1,2] In the literature three factors were found that may play a role: localization with a high risk of trauma, local factors such as bacteria (either infection or colonization) (Figure 1) and tissue hypoxia caused by a fast growing IH that outreaches its blood supply (Figure 2).[2,3] In the past, few studies were carried out that investigated ulcerating IH. The purpose of the present study was to get a better insight into the clinical characteristics of ulcerated IH and non-ulcerated IH in a retrospective analysis of hemangioma patients, who visited our multidisciplinary hemangioma-study group over the past 10 years. For this extensive patient group, the known differences between ulcerated and non-ulcerated IH from earlier studies were investigated again and supplemented with other characteristics that were also considered important. Better knowledge of the differences between ulcerated and non-ulcerated IH will hopefully deliver better insight into the pathogenesis and treatment of this distressing problem in young children.

Figure 1
Ulcerated hemangioma involving the scrotal skin.

Figure 2
Large segmental hemangioma on the arm with multiple localizations of ulceration.

Patients and methods

Patients

A retrospective analysis was performed of all IH at the Radboud University Medical Centre Nijmegen (UMCN), the Netherlands, from 1997 to 2007. The medical records and photo documentation of 465 patients with a hemangioma were reviewed. The following information

was obtained from each patient file: *Hemangioma:* ulceration or not (1), number of IH per patient (2), size (3), anatomic localization (4), type (5), age at time of discovery (6). *Ulceration:* phase of growth at time of ulceration (7), duration (8). *Other:* sex (9), prematurity/gestational age (10), birth weight (11), multiple gestation (12), (transcervical) chorionic villus sampling (13), atopic constitution/dermatitis (14).

Analysis

Data from the patient files were transported into a database and analyzed to define the characteristics of the study group and subsequently the differences between the ulcerated and non-ulcerated IH. The numeric data were reported as mean ± SEM. For statistical analysis the t-test for unpaired values was used. The other non-numeric data were analyzed with the Fisher exact test. The two tailed hypothesis was employed to interpret data. A p-value ≤ 0.05 was regarded as statistically significant.

Results

After registration of data mentioned above, the files were divided in two groups: IH with active or past ulceration versus IH which never ulcerated. Comparison between the two groups was carried out. In the description below, the results of all examined characteristics are reported.

Ulcerated *vs*. non-ulcerated IH

A total of 465 records of patients were investigated. Of these 107 (23%) were diagnosed with an ulcerated IH *versus* 358 (77%) patients with one or more non-ulcerated IH. The patients with an ulcerated IH had a total of 235 IH, 108 ulcerated and 127 non-ulcerated. The 358 patients with only non-ulcerated IH had a total of 815 IH.

Number of IH

The average number of IH in the group of patients with an ulcerated IH was 2.2 (SEM ± 0.5). For the patient-group with only non-ulcerated IH this mean number was 2.3 (SEM ± 0.3). This difference is not statistically significant ($p = 0.9$).

Size of IH

The surface of the IH was measured with a tape-measure in 2 perpendicular directions, using the maximum diameter in each to calculate the final surface. The mean length and width of the ulcerated IH were respectively 5.1 cm. (SEM 0.4) and 4.3 cm. (SEM 0.3). For the non-ulcerated IH this was 2.1 cm. (SEM 0.1), and 1.8 cm. (SEM 0.1). This shows that the ulcerating IH had a significantly larger surface than the non-ulcerated IH (28.6 cm^2 *vs*. 6.0 cm^2, $p < 0.05$). Data concerning the size were only known from 51.6% of the ulcerated IH and 62.0% of the non-ulcerated IH.

Table 1 Localization

Localization		Ulcerated (%)	Non-ulcerated (%)
Extremities		21.3	20.8
Head and neck		47.2	52.9
Torso		12.0	22.4
Perineum	diaper area	12.0	1.5
Buttock	diaper area	6.5	1.4
Groin	diaper area	0.9	0.6
Sacral region		0	0.5

Anatomical localization

The IH were classified in 7 different region categories: (1) extremities, (2) head and neck, (3) perineum, (4) groin, (5) trunk, (6) buttock and (7) sacral region. In general, most IH were located on the head and neck region, the extremities and trunk. The predilection area for ulceration was the head and neck region, but also IH in the perineal and buttock area often turned out to be ulcerating. Ulcerated IH were significantly more often localized in the diaper area ($p < 0.05$) (Table 1). The localization of the IH was not uniformly documented. 29.5% of the non-ulcerated IH had an unknown localization.

Subtype of IH

IH were divided in 3 clinical subtypes; (1) superficial, (2) deep and (3) mixed IH with involvement of both epidermis and subcutis. When both ulcerated and non-ulcerated IH were compared, ulceration was more frequently seen in the IH with a superficial component. 78.2% of the ulcerated IH had a superficial component compared to 61.1% of the non-ulcerated IH. This was a significant difference ($p < 0.05$). The deep IH ulcerated significantly less frequently ($p < 0.05$) (Table 2). It was known whether they were superficial, deep or mixed for 65.0% of the ulcerated IH and 64.9% of the non-ulcerated IH.

Added to this, IH can be divided in morphological subtypes; localized and segmental IH can be distinguished. Localized IH are focal tumor like lesions. The less commonly occurring segmental IH tend to be more plaque-like and involve a region or segment of skin. Ulcerated IH had a segmental distribution significantly more often (29.3%) compared to 2.1% of the non-ulcerated IH ($p < 0.05$) (Table 2). Data concerning the distribution were available for 85.2% of ulcerated IH and 95.5% of non-ulcerated IH.

Phase of ulceration

The growth characteristics of IH can be divided in phases: proliferation phase (0-9 months), a short plateau phase and involution phase (until the age of 10-12 years). Growth

Table 2 Subtypes

Clinical type	Ulcerated (%)	Non-ulcerated (%)
Superficial total	78.2	61.1
Deep	1.5	25.3
Mixed	20.3	13.6
Morphological type		
Segmental	29.3	2.1
Localized	70.7	97.9

characteristics of IH in an individual infant may vary. In this study the phase in which the ulceration occurred was investigated. Most frequently, ulceration took place in the proliferation phase (83.1%), but also in the involution phase (15.3%) and the plateau phase (1.7%). It was known in which phase the ulceration had taken place for 54.6% of the IH.

Duration of ulceration

In 20.4% of cases the duration of ulceration was well documented and varied between 4 days and 7 months, with a mean of 8.1 weeks (SEM 1.6).

Sex

For the patients examined the sex distribution was 67.3% girls and 33.7% boys, which makes a ratio of 1:2. For the group of patients with an ulcerated IH the number of male and female patients was respectively 27 (25.2%) and 80 (74.8%), a ratio of 1:3. This means a tendency to significantly more females with an ulcerated IH compared to female patients with just non-ulcerated IH ($p = 0.08$) (Figure 3).

Prematurity/gestational age

The mean gestational age in the group with an ulcerated IH was 35.0 weeks (SEM 0.6). For the group with just non-ulcerated IH the mean gestational age was 36.7 weeks (SEM 0.47). This was significantly different ($p = 0.04$).

Prematurity in this study was defined as birth before 37 weeks of gestation. Analysis of the number of prematures in both patient groups, resulted in 61.1% prematures in the patient group with ulcerated IH compared to 26.5% of the children in the patient group with only non-ulcerated IH. This was a significant difference ($p < 0.05$) (Figure 3). It was known whether or not they were premature for 33.6% of the patients with an ulcerated IH and 27.4% of the children with non-ulcerated IH.

Subsequently the degree of the prematurity for both groups was compared. For the premature children with ulcerated IH the mean gestational age was 33.1 weeks (SEM 0.6).

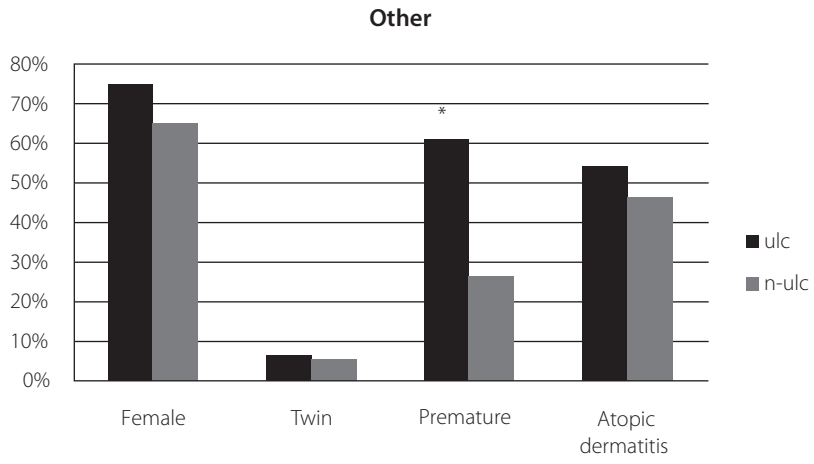

Figure 3 Other

For the patients with just non-ulcerated IH this mean age was 32.7 weeks (SEM 0.6). This was not significantly different (p = 0.7). For 30.8% of the children with an ulcerated IH, the exact gestational age was known, compared to 20.1% of the children with no ulcerated IH.

Birth weight

The mean birth weight found for the patient group with an ulcerated IH was 2649 grams (SEM 140.7) and 3022 grams (SEM 189.3) for the other patient group with only non-ulcerated IH. These indicates a tendency to a significantly lower birth weight for children with ulcerated IH (p = 0.06).

Birth weight was documented for 18.7% of the patients with an ulcerated IH and for 20.1% of the patients with just non-ulcerated IH.

Multiple gestation

For both patient groups it was registered whether or not they were part of twins. In the total study group 5.6% of the patients were part of twins. For the patient group with an ulcerated IH this was 6.5%, for the patient group with non-ulcerated IH this was 5.3%. This is not a significant difference (p = 0.4) (Figure 3).

Chorionic villus sampling

In this study no chorionic villus sampling was performed in either patient group.

Atopic dermatitis

In the patient group diagnosed with an ulcerated IH, 54.2% of the children were also diagnosed with atopic dermatitis, in the patient group with only non-ulcerated IH this was

46.5% (Figure 3). This is not a significant difference (p = 0.62). Overall, not all patient files gave clear information about the presence of atopic dermatitis in the patient. Only for 22.4% of the patients with an ulcerated IH versus 12.0% of the patients with non-ulcerated IH was it noted.

Discussion

In this study, ulceration was found in 23% of the IH patients compared to 5-13% described in literature.[1,2] This can be explained by the fact this study was carried out in an academic centre with a specialized multidisciplinary hemangioma team that serves as a tertiary centre for patients with difficult (ulcerating) IH.

When overviewing the characteristics described, there were no differences concerning the number of IH per patient between the patient group with one or more ulcerated IH versus the group with just non-ulcerated IH. With respect to size, localization and type of IH, some differences could be recognized, comparable to the recently published results of the American cohort studied by Chamlin et al. in 2007.[4]

Ulcerated IH were significantly larger than non-ulcerated IH. In line with this result, segmental IH, which in general cover a substantial skin surface, ulcerated more frequently. Probably, larger IH run a greater risk of becoming mechanically damaged by friction resulting in ulceration. With respect to localization, ulcerated IH were mostly localized in the head and neck region, but the diaper area was also a localization with an enlarged risk for ulceration. It seems that traumas like friction and contamination/maceration are more common in these areas. With respect to clinical types, IH with a superficial component were frequently ulcerated as opposed to deeper IH that seldom ulcerated.

Taken together, epidermal involvement and susceptibility to trauma and maceration seem to play a role in pathogenesis of ulceration in IH. These characteristics are connected with the barrier function of the skin. If this is impaired, there seems to be a greater risk of ulceration.[2] In view of this, it was interesting to compare the incidence of atopic dermatitis, in which the barrier function is also impaired, between the patient groups with and without ulcerated IH, but no significant difference could be found. Additional prospective studies need to be done to confirm or reject this assumed interesting relationship.

The phase in which ulceration mostly took place was obviously the proliferation phase. This is also known from the literature.[2,4,5] The possible reason given in literature is the outgrowth of the blood supply in the fast growing IH, resulting in central necrosis.[6, 7] The mean duration of ulceration turned out to be about 8 weeks. It must be stated that, because our centre is a referral centre for complicated IH, this might be overestimated in this study. Besides this, the exact duration is often unknown because of the difficulty of exact registration. Patients who do better are often lost to follow-up and/or return to the general practitioner. Therefore a prospective study should be carried out as well.

In addition, demographic characteristics were studied. From the literature it is known that the female to male rate for IH patients is 2.5-4 to 1.[2] In our study it was found that the group with ulcerated IH comprised a higher percentage of female patients compared to the patients with non-ulcerated IH. In former studies, hemangioma patients were more likely to be premature. Which could be in relation with the fact that a greater percentage of premature children are female.[8-11] In our study it was observed that the patients with ulcerated IH were more often premature. The mean gestational age of the children with ulcerated IH was also lower. Besides this, the mean birth weight of patients with ulcerated IH also seemed lower although with only a tendency to significance. This last result is also known from the literature.[12] This could mean that prematurity and low birth weight increase the risk of ulceration.

It was striking that in all twin cases, the other twin was unaffected. The number of twins in the studied cohort (5.6%) was higher than the 1.6% twins in the general population, which is in line with a higher incidence of prematurity and lower birth weights in this group. Although ulceration was not more frequent in twins with an IH.

Conclusion

Ulceration is a frequent complication affecting 23% of our studied patients. This high incidence of ulceration makes this Dutch cohort, containing high rates of complicated IH, very appropriate for evaluating the characteristics of ulcerated IH. In summary, larger IH with a superficial component in areas more predisposed for contamination are more at risk for ulceration. We found a high incidence of ulceration in the large group of IH in the head and neck region but also a statistical significantly higher percentage of ulcerated IH in the perineum and buttock area. These results will, however, give us more insight into the unknown and multifactorially determinated pathogenesis of ulceration in IH. Besides this, it will probably make it possible to predict whether or not an IH might ulcerate.

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3.2

Propranolol, a very promising treatment for ulceration in infantile hemangiomas: a study of 20 cases with matched historical controls

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Summary

Background Ulceration is a common but poorly understood complication of infantile hemangiomas (IH) that is difficult to control.
Objective To investigate the possible role of monotherapy with propranolol for ulcerating IH.
Methods Propranolol was given to 20 patients with IH, who suffered from ulceration at the start of treatment (mean age at onset of treatment, 3.5 months; standard error of the mean: 0.4). After cardiac screening, propranolol was administered in a progressive schedule to 2 to 2.5 mg/kg per day, divided in 3 doses. Blood pressure, heart rate, and fasting glucose levels were monitored during the first 3 days in hospital and, in the absence of complications, treatment was continued at home until the age of approximately 1 year. The 20 propranolol-treated patients were matched to patients from a historical control group, seen before the 'propranolol era'. These matches were randomly made by using clinical pictures based on type, location and size of the IH, extent of ulceration, and age at the start of ulceration.
Results The time to complete healing from the onset of ulceration was significantly shorter for the propranolol-treated patients, compared with the control group (8.7 vs. 22.4 weeks; t-test: $p < 0.015$). In the propranolol group, a tendency to shorter ulceration duration was seen in patients starting propranolol at an earlier stage of disease.
Limitations The study was limited by the partially retrospective design and the small number of patients.
Conclusion Propranolol reduces the duration of ulceration in IH and seems to be more effective when started in an early phase. We propose propranolol as the treatment of first choice for ulcerating IH.

Introduction

Infantile hemangiomas (IH) occur in approximately 10% to 12% of children younger than 1 year of age. The most common complication is ulceration, possibly affecting 5% to 13% of children with IH.[1,2] Ulceration is nearly always painful, and this leads to problems with eating and sleeping. There may also be bleeding and infection requiring treatment with oral antibiotics. Finally, ulceration heals with scarring, leading to functional problems and cosmetic disfigurement.[3-6] There is no uniform approach to treatment in the literature. In addition to all kinds of wound dressings, topical or oral antibiotics and pain management, treatment with oral corticosteroids, vincristine, interferon, flashlamp pulsed dye laser therapy, and surgical options have been described, often with disappointing results.[1,5,7]

Propranolol was recently introduced as a promising treatment for complicated IH.[8] There have been several case reports of propranolol therapy for ulcerating IH, but no comparative studies have been published.[8-10] In our study, the role of this nonselective beta-blocker was explored by treating 20 patients with an ulcerating IH in the proliferation phase and comparing this patient group with similar historical controls.

Patients and methods

Patients

An observational analysis was performed of IH patients treated with propranolol at the Radboud University Medical Centre Nijmegen (UMCN), the Netherlands, from October 2008 to March 2010. The medical records and photo-documentation of 56 infants were reviewed and all patients with ulceration were selected. Twenty patients suffered from ulceration at the start of the treatment (mean age at onset of treatment: 3.5 months, standard error of the mean [SEM] 0.4). Ulceration was not always the main indication for propranolol treatment.

Ulceration was defined as a break in the continuity of the surface epithelium with or without infection.

The 'total ulceration time' was defined as the time from the first sign of ulceration until complete healing, without complete healing in the intervening period. 'Long-lasting ulceration' was ulceration with a longer duration than the mean ulceration time. 'Early starters' were patients started on propranolol before the mean age at onset of treatment. At inclusion, a clinical evaluation including physical examination, renal function tests, an electrocardiogram, and echocardiography was performed to exclude contraindications to propranolol treatment. Propranolol was administered in the hospital with a starting dose of 0.7 to 1.0 mg/kg per day, divided in 3 daily doses, increasing over a 3-day period to 2.0 to 2.5 mg/kg per day. Blood pressure, heart rate, and fasting glucose levels were monitored during the first 3 days. In the absence of complications, treatment was

continued at home until about the age of 1 year. The patients were evaluated every 6 weeks after starting treatment with propranolol, and more often if necessary. In the final phase of treatment, clinic visits were extended to every 3 months. During the study period, no other systemic treatment modalities, apart from oral antibiotics or analgesia, were administered.

Historical data of IH patients from our center during the period 1997 to 2007 were analyzed retrospectively and used to establish controls.[11]

Ulceration was present in 107 of these 465 IH cases. Using clinical pictures and medical records, two investigators, who were blinded as to the clinical outcomes, made a random selection of 20 patients with a comparable ulcerating IH. The comparisons were based on age at onset of ulceration, type, location and size of the IH, and extent of ulceration. Follow-up evaluations in this patient group were similar to those of the propranolol-treated group.

Analysis

In the event of missing data in the control group, an interview with the parents by telephone was performed. The maximum age of the patient at the time of the interview was 5 years. Data from the patient-files were transported into a database and analyzed to define the characteristics of the study group. The numeric data were reported as mean plus or minus SEM.

For statistical analysis the t-test for unpaired values was used. The other non-numeric data were analyzed with the chi-square test. A two-tailed hypothesis was employed to interpret data. A p-value less than or equal to 0.05 was regarded as statistically significant.

Results

Propranolol group

Patient characteristics. The 20 patients (Table 1) with an ulcerating IH had a total of 78 IH, with an average number of 3.9 IH per patient (SEM 1.7).

Of this group, 16 (80%) were girls. The mean gestational age was 36.8 weeks (SEM 0.7). The mean birth weight was 3017 grams (SEM 195). Nine patients (45%) were born prematurely (before 37 weeks' gestation), one with extreme prematurity (gestational age 30.7 weeks).

The anatomic location of the ulcerating IH was as follows: 14 (70%) in the head and neck region, 1 on the shoulder, 1 on the arm, and 4 (20%) in the diaper region. The following clinical IH subtypes were recorded: 14 (70%) superficial nodular, 4 (20%) superficial macular and 2 (10%) mixed; no IH had an exclusively deep growth pattern. Morphological subtypes included 14 (70%) with a localized and 6 (30%) with a segmental distribution. The mean age at which the IH was first noted by the parents was 6.4 days (SEM 2.4).

Propranolol. Ulceration was the main indication for treatment with propranolol in 18 cases (90%).

In these patients, painful ulceration resulted in problems with drinking, sleeping, defecation or restriction of movement. In the two other infants, tachypnea and inspiratory stridor due to airway obstruction were the primary indications for treatment.

The mean age of starting propranolol was 3.5 months (SEM 0.3). At the time of data analysis, 19 patients had discontinued propranolol and the remaining infant was in the final phase of treatment. The average treatment duration for the 19 patients was 9.1 months (SEM 0.6).

Within the first 3 days of starting treatment in the hospital, a decrease in redness and tenseness of the IH was observed in all cases. This effect was sustained over the remaining treatment period. Four (21.1%) of the 19 patients who completed treatment showed some regrowth and slightly increased redness after stopping propranolol, but there was no recurrence of ulceration. In one patient propranolol was restarted because of the mass effect of the IH.

Nine patients (45%) experienced no adverse effects at all. The parents of 11 patients reported temporary drowsiness/tiredness (n = 6), restless sleeping (n = 2), cold extremities (n = 6), poor feeding (n = 2) and gastrointestinal complaints (diarrhea, vomiting) (n = 1).
Six patients (30%) were treated with an oral pain medication (acetaminophen) and 7 patients (35%) were treated with oral antibiotics. Eleven patients (55%) were additionally treated with topical ointments and wound dressings either before or during propranolol treatment. No other systemic treatment modalities for the IH (such as systemic corticosteroids) were necessary.

Ulceration

All patients had an ulcerating IH at the time of starting propranolol. The mean age of the patients at the start of ulceration was 2.3 months (SEM 0.3). Complete healing was obtained after an average total ulceration time of 8.7 weeks (SEM 8.5).

In the propranolol-treated group, a tendency to a shorter ulceration time was seen in patients starting propranolol at an early age. Seven of the 10 'late starters' (70%) (started propranolol at >3.5 months of age) had a 'long lasting ulceration' (>8.7 weeks) compared with only 2 (20%) of the 10 'early starters' ($2 = 5.051$, $df = 1$, $p = 0.025$).

Most parents reported a decrease in pain within a few days after initiation of propranolol.

Historical control group

The historical control group consisted of 20 comparable cases from a historical group treated before the propranolol era (see Table 1).

These control patients had similar complications from an ulcerating IH, including problems with eating, sleeping, defecation, and restriction in movement due to pain. Five patients (25%) in the control group were treated with oral corticosteroids, 1 (5%) with

Table 1 Clinical characteristics of 40 patients with ulcerated hemangioma

Propranolol group	Gender	Location	Clinical subtype	Morphological subtype	Oral AB	Other systemic tx	Duration of ulceration (wk)
1a	F	Face/cheek/mouth	Sup/Nod	Loc	+	-	3*
2a	F	Diaper area (labium majus)	Sup/Nod	Loc	-	-	13†
3a	F	Diaper area (buttocks)	Sup/Nod	Loc	+	-	2
4a	M	Scalp	Sup/Nod	Loc	+	-	13
5a	F	Lip	Sup/Nod	Loc	-	-	11
6a	M	Shoulder	Sup/Nod	Loc	-	-	4
7a	M	Face	Mixed	Segm	-	-	5
8a	F	Face (nose/cheek)	Mixed	Segm	-	-	7
9a	F	Ear	Sup/Nod	Loc	-	-	19
10a	F	Face	Sup/Mac	Segm	+	-	5
11a	F	Leg/buttocks	Sup/Mac	Segm	-	-	6
12a	F	Face (lip/mouth)	Sup/Mac	Loc	-	-	15
13a	F	Buttocks	Sup/Mac	Loc	-	-	8
14a	M	Scalp	Sup/Nod	Loc	-	-	10
15a	F	Scalp	Sup/Nod	Loc	+	-	12
16a	F	Lip	Sup/Nod	Loc	-	-	4
17a	F	Arm	Sup/Nod	Loc	-	-	4
18a	F	Scalp	Sup/Nod	Loc	+	-	19
19a	F	Lip	Sup/Nod	Segm	-	-	1
20a	F	Face (neck)	Sup/Nod	Segm	+	-	13

+, Prescribed; -, not prescribed; AB, antibiotics; Loc, localized; PDL, pulsed dye laser; Sup/Mac, superficial/macular; Sup/Nod, superficial/nodular; tx, therapy.

*Patients shown in Fig 1.

†Patients shown in Fig 2.

pulsed dye laser therapy, 12 (60%) with one or more oral antibiotics, and all 20 with a variety of local wound dressings and ointments. The mean age of the patients at the start of ulceration was 2.7 months (SEM 0.3), not dissimilar to the propranolol-treated group ($p = 0.49$). The mean ulceration time for the control group was 22.4 weeks (SEM 5.2). The outliers in both the propranolol and control groups were patients with ulceration in skin folds and locations with extensive exposure to friction, maceration, and external factors (e.g. feces, urine, food), which delayed the healing process.

	Control group	Gender	Location	Clinical subtype	Morphological subtype	Oral AB	Other systemic therapy	Duration of ulceration (wk)
	1b	F	Face (cheek/mouth)	Sup/Nod	Loc	-	Prednison	6*
	2b	F	Diaper area (buttocks)	Sup/Nod	Loc	+	-	30†
	3b	F	Diaper area (buttocks)	Sup/Nod	Loc	+	-	96
	4b	F	Scalp	Sup/Nod	Loc	+	-	16
	5b	F	Lip	Sup/Nod	Loc	-	-	24
	6b	F	Shoulder	Sup/Nod	Loc	+	-	4
	7b	M	Face	Mixed	Segm	+	-	20
	8b	F	Face (cheek/ear)	Sup/Nod	Segm	+	-	36
	9b	M	Neck	Sup/Nod	Loc	-	-	4
	10b	F	Face	Sup/Mac	Segm	+	-	20
	11b	M	Buttocks	Sup/Mac	Segm	+	-	4
	12b	F	Face (ear/nek)	Sup/Mac	Loc	+	Prednison PDL	56
	13b	M	Buttocks	Sup/Nod	Loc	-	Prednison	24
	14b	F	Neck	Sup/Nod	Loc	+	-	10
	15b	F	Scalp	Sup/Nod	Loc	-	-	2
	16b	F	Lip	Sup/Nod	Loc	-	Prednison	44
	17b	F	Arm	Sup/Nod	Loc	-	-	6
	18b	F	Scalp	Sup/Nod	Loc	+	-	10
	19b	F	Beard area/lip	Sup/Nod	Segm	+	Prednison	12
	20b	M	Face (neck)	Sup/Noc	Segm	-	-	24

Comparison IH groups: Ulceration time

The t-test for unpaired values showed a significant difference in mean ulceration duration between the 20 patients treated with propranolol and the 20 cases in the control group, including both patients treated with supportive care only and with systemic therapy (8.7 vs. 22.4 weeks; $t = 2.6$, $df = 38$, $p = 0.012$, 95% confidence interval, 3.2-24.2).

An additional analysis was performed to compare the 20 patients in the propranolol group with the 5 patients in the historical group treated with oral corticosteroids. This comparison showed a significant difference in mean ulceration time (8.7 vs. 28.4, $t = 3.88$, $df = 23$, $p = 0.001$, 95% confidence interval 9.2-30.2).

Finally, a comparison was made between the 20 patients treated with propranolol and the 15 patients in the control group treated with supportive care only (oral antibiotics and wound dressings). This also showed a significant difference (8.7 vs. 20.4, t = 2.17, df = 33, p = 0.037, 95% confidence interval 0.7-22.7).

An illustration of the duration of ulceration in patients treated with propranolol compared with historical controls is given in Figure 1 and 2.

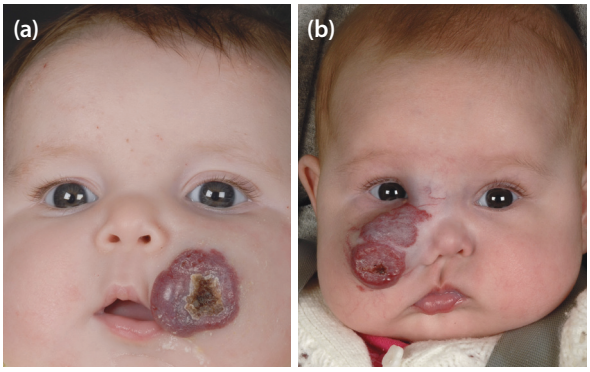

Figure 1
(a) Ulcerating IH on left cheek, before treatment with propranolol: total ulceration time 3 weeks (patient 1a in Table 1). **(b)** Ulcerating IH on right cheek, before treatment with oral corticosteroids, not treated with propranolol:.Total ulceration time 6 weeks (patient 1b in Table 1).

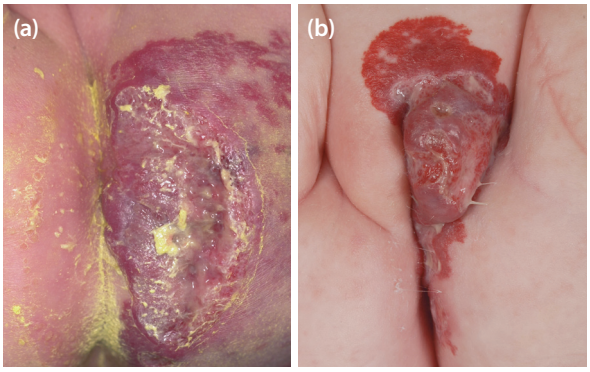

Figure 2
(a) Ulcerating IH on left labium majus, before treatment with propranolol: total ulceration time 13 weeks (patient 2a in Table 1). **(b)** Ulcerating IH on left buttock, not treated with propranolol or oral corticosteroids: total ulceration time 30 weeks (patient 2b in Table 1).

Discussion

A review of the literature reveals no evidence-based or uniformly accepted treatment plan for ulcerating IH. This is in part because of the unclear pathogenesis of the ulceration but also to the variable course of ulceration and involution of IH.[6] The generally accepted triad for treatment of ulcerating IH is (1) wound care, (2) topical or oral antibiotics, and (3) adequate pain management. In addition, various therapeutic agents aimed at promoting involution of the IH have been used (e.g., corticosteroids, vincristine, interferon, flashlamp pulsed dye laser and surgical intervention), often with unsatisfactory results.[1,5,7,12,13] There is a need for a new treatment modality to control this challenging complication more effectively.

The extraordinary response of infantile IH to propranolol, first reported in the New England Journal of Medicine by Léauté-Labrèze et al, introduced a new therapeutic option.[8] Our multidisciplinary hemangioma treatment group subsequently initiated propranolol treatment for complicated IH, including ulcerated lesions. There was almost immediate cessation of proliferation in every patient, leading to considerable shortening of the natural course of IH. This termination of proliferation had a direct effect on the duration of ulceration. Recently, a few case series of patients with ulcerating IH successfully treated with propranolol have been described.[8-10]

As a great number of patients with complicated IH are treated at our tertiary referral center, it was possible to select a similar control patient from our historical database for each of the propranolol-treated cases. After the two groups were compared, it was found that the mean ulceration time was significantly shorter for the patients treated with propranolol compared with the historical matched control group (8.7 vs. 22.4 weeks). When the propranolol-treated patients were compared with patients in the control group treated with systemic corticosteroids or with supportive management only, a significantly shorter ulceration time for the propranolol group was still found. The relatively long ulceration time for both the propranolol group (8.7 weeks) and the control group (22.4 weeks) may be explained by the fact that, as a tertiary referral center, we treat more complicated IH with larger ulcerations. Ulceration is a dynamic process and new adjacent ulceration may develop before healing of the first area of ulceration. These consecutive lesions mean that some ulcerations take a long time to heal completely.

The effect of propranolol on ulceration in IH also seemed to be related to the time of onset of treatment. Initiation earlier in the proliferation phase nearly always resulted in a tendency to faster healing. Only 2 (20%) of the early starters had a prolonged ulceration compared with 70% of the late starters. From earlier studies it is known that larger, more superficial IH in areas susceptible to trauma and contamination are more likely to ulcerate.[11,14] Possibly, the best way to treat these potentially complicated IH is to start propranolol early in the proliferation phase to prevent ulceration.

The observation that propranolol is very effective in the treatment of ulcerating IH compared with historical controls should be discussed in light of the limitations of this

study. The data were obtained retrospectively for the control group, but were recorded by physicians unaware of the specific hypothesis of the study. The risk of confounding is a threat to the validity of observational studies. The strongest evidence that propranolol is an effective treatment for ulcerating IH would be provided by a randomized placebo-controlled trial. However, the undoubted clinical efficacy of propranolol in treating IH now makes this type of study almost unethical.

In our opinion, clinically useful conclusions can be drawn despite the limitations of this study design. We propose that propranolol should be the treatment of first choice for seriously ulcerating IH.

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4

Parental experiences with the treatment of complicated infantile hemangioma

4.1

Parental experiences with propranolol versus oral corticosteroids for complicated infantile hemangioma, a retrospective questionnaire study

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Abstract

Background Infantile hemangiomas (IHs) are common and mostly emerge in the head and neck area. Recently, propranolol has been replacing oral corticosteroids (OCS) as the main treatment modality.

Objectives The target of this study was to explore the impact of treatment, contentment with treatment outcome and quality of life for families and patients with cervicofacial IHs, treated with propranolol versus OCS.

Materials and Methods This case control study was performed using questionnaires administered by a phone interview. Parents of 16 patients with a cervicofacial IH treated by OCS and 16 patients with an IH of similar localization and overall severity treated with propranolol were interviewed. The questions concerned the impact of treatment at different time periods and the contentment with treatment results. Parents were also asked to give a quality of life (QoL)-score (1 to 10) for different time-points.

Results Parents from the OCS group seemed to feel significantly more worried during treatment. Moreover, parents from the propranolol group perceived less negative impact on normal life issues, including work and vaccination of their child. During and after treatment, the parents of propranolol treated IH patients gave significantly higher Qol-scores.

Conclusion Propranolol seems to change the impact of IHs, their treatment and the quality of life. Propranolol treatment interferes less with normal issues in daily life, compared to OCS. These findings underline propranolol as the first-choice treatment for life- or function-threatening IHs.

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors of infancy and childhood with an incidence ranging from 2-10%.[1] About sixty per cent of these benign tumors emerge in the cervicofacial area.[2]
IHs go through different phases with most notably, initial rapid and massive growth followed by slow involution. After involution, normal or cosmetically satisfactory skin is restored in nearly 50% of untreated patients.[3,4] In the other 50% the skin shows atrophy, laxity, telangiectasia, pigmentation changes, scarring or alopecia.[3]

Although the majority of IHs implicate no immediate or long-term threat, a significant minority can cause serious morbidity. Possible complications are painful ulceration, amblyopia in periorbital localization, feeding difficulties in perioral localization, breathing problems in airway IH, hearing problems in periauricular localization and disfigurement.[5] Deformities of the face may result in psychosocial distress in children and their parents.[6] It is believed that disfigurements can lead to negative reactions from strangers, social stigmatization, sadness, stress and low self-esteem.[7] Parents may start to isolate their children from social interaction to protect them(selves) from hurtful comments.[6]

Intervening in the natural course of an IH may be indicated in case of (potential) complications or expected very poor aesthetic outcome.[5] Until 2008, different therapies for IH existed, each with their own potentially dangerous side effects. Among these, oral corticosteroids (OCS) have long been the mainstay of treatment, with gastro-intestinal upset, Cushingoid appearance, hypertension and temporary growth retardation as part of the side effect profile.[8-10]

A novel approach in IH treatment is propranolol, an adrenergic beta-antagonist that has been widely used in (pediatric) cardiology, which was serendipitously discovered in 2008, like OCS were in 1963.[11,12] Case series and a recent randomized controlled trial of propranolol report spectacular responses with fewer side effects than previous treatments. The most important side effects reported in literature are hypotension, pulmonary symptoms and hypoglycemia.[13-15] In every day practice, a careful indication shift can be seen for an active approach (with propranolol) of IHs: from function-threatening IHs towards severely cosmetically disturbing (large facial) IHs.

Despite the current widespread use of propranolol, so far, no study has explored the impact of propranolol treatment on daily family life of IH-children and the quality of life (QoL), during and after this period, in comparison to the former approach with OCS. The contentment of the parents with the treatment outcome after propranolol or OCS was studied as well. These data are also important for further implementation of propranolol in daily practice.

Materials and methods

Patients

Our tertiary referral centre started treating IH patients with propranolol in 2008. From our former cohort of more than 100 propranolol treated IH patients, the children with a cervicofacial IH were selected by reviewing photo-documentation and medical records. On the basis of these propranolol-treated patients, OCS-treated IH patients from our cohort from before the propranolol era with a comparable IH were selected. Only patients that had completed treatment were included. The best possible clinical matching between both groups was sought based on: localization, subtype, size, ulceration and overall severity. All IH in both groups were in the proliferation phase at the start of treatment. Two patients with PHACES were included and matched. Sixteen good matches could be made. This method of case control study has been used previously.[16] For both patient groups the clinical endpoints were stop of growth and start of involution of the IH, volume reduction and improvement of functionality (e.g. in case of earlier visual impairment). These endpoints were subjectively assessed by the treating physician at that time and were reached for all patients in both patient groups at the end of treatment.

Treatment

Prior to both treatments, the parents were extensively informed about the possible side effects of treatment.

OCS: A mean dosage of 2-4 mg/kg/day Prednisolone oral suspension, in 2 doses was given in a course of 6-8 weeks (range 4-12 weeks) that was repeated 1-2 times in case of insufficient efficacy. In Table 1 the total period from the start of the treatment till the end of the (last) treatment is represented.[14,17]

Propranolol: After cardiologic screening the starting dosage was propranolol oral suspension 0.7-1.0 mg /kg /day, in three divided doses. The dose was gradually increased to the total target dosage of 2.0-2.5 mg/kg /day, divided in three doses. Guided by body weight, propranolol was adjusted to the target dosage until the age of 9 months after which the dose was no longer increased. Treatment was continued during the proliferation phase (age 12-18 months) and gradually tapered in 2-3 weeks.[18] Detailed information on the treatment protocol can be found in a previous report.[19]

The median time span between start of treatment and time of study is 7.0 years (range 4.3-12.6) for the OCS group and 2.1 years (range 1.2-2.5) for the propranolol group.

Study design with questionnaires

Data in this study were obtained from patient files and an interview by telephone. According to the Dutch law (WMO; Wet medisch-wetenschappelijk onderzoek met mensen; Medical Research Involving Human Subjects Act), review of the study by the Ethics Committee of Radboud University Nijmegen Medical Centre was not needed. This was confirmed after

consultation of the committee and informed consent from all parents was considered sufficient.

An information letter was sent to all parents explaining the purpose of this study and asking their participation in an interview by telephone. Informed consent was obtained from all parents.

Interviews of 32 parents were all carried out by the same investigator (JZ); not blinded. The interview consisted of a medical information form and a questionnaire on impact of IH treatment and contentment with treatment outcome. In a second questionnaire, parents were asked to indicate a score for their quality of life during different treatment periods. The interview took about twenty minutes per patient.

Medical information form

This form included questions about the size, localization and complications of the IH and treatment duration. Besides demographic data, information about pregnancy, delivery and birth weight were asked.

Questionnaires

Questionnaires were developed by the researchers in collaboration with the Radboud Expert Centre for Psychology & Medicine. The first questionnaire addressed the impact of IH treatment and contentment with treatment outcome and consisted of 32 questions with a 5 point Likert scale (totally disagree – disagree – neutral – agree – totally agree; score 1 to 5). The questions are divided into five time intervals: prior to treatment, during treatment, after treatment (directly and after three months) and expectations for the future. The second questionnaire was used to obtain a quality of life (QoL)-score (1 to 10) from the parents for the periods prior to, during and after treatment and also for the final result, taking their worries and problems or results of treatment into consideration. The higher the score, the better the period or the result was.

Analysis

Statistical Package for the Social Sciences (SPSS) 18.0 (SPSS Inc., Chicago, IL, U.S.A.) was used to analyze data.

Group characteristics were explored and numeric data stated as mean plus standard deviation (SD). For testing all items of the questionnaires, we used the independent sample t-test. Given the explorative character of the study and the multiple statistical analyses performed, a more stringent α-level was chosen (0.01) to analyze the impact of treatment and contentment with treatment outcome. For the questions concerning quality of life-scores the α-level was set at 0.05.

Results

Patient and treatment characteristics

Demographic and clinical characteristics of included patients are stated in Table 1. These characteristics show no significant differences (p-values > 0.05) between both treatment groups, except for current age of children and treatment duration, inherent to these treatment modalities.

Table 1 Group characteristics of 16 matched patients

	Propranolol (n = 16)	Oral corticosteroids (n = 16)
Respondents/parents		
Mean age (years)	35 (SD 3.4)	38 (SD 4.3)
Gender	14 F / 2 M	13 F / 3 M
Origin	15 Netherlands / 1 Germany	16 Netherlands
Mean time of pregnancy (weeks)	38.5 (SD 1.9)	38.8 (SD 2.7)
Patients		
Minimum age (months)	19	55
Maximum age (months)	34	157
Gender	10 F / 6 M	12 F / 4 M
Mean birth weight (grams)	3410 (SD 766.0)	3143 (SD 1548.9)
Mean number of IHs	1.56 (SD 1.5)	1.63 (SD 1.4)
Mean age at start treatment (months)	3.3 (SD 1.2)	2.9 (SD 0.8)
Mean age of complication* (months)	2.7 (SD 1.1)	2.1 (SD 1.4)
Mean treatment duration (months)	9.6 (SD 2.4)	5.8 (SD 3.9)

F = Female, M = Male, *Mean age at which a complication of the IH occurred, e.g. ulceration, bleeding and visual impairment.

IH characteristics including localization, clinical and morphological subtype of treated IHs, as well as their treatment duration and possible ulceration, are given for each matched patient-pair in Table 2.

Adverse reactions observed during treatment in both groups were in line with the profile of adverse events of both treatments as reported in literature.[9,20]

Questionnaires

Results from the questionnaire on the impact of IH treatment and contentment with treatment outcome are presented in Table 3 and the quality of life scores in Table 4.

Prior to treatment: No significant differences between treatment groups existed. Also, the mean QoL-score for this period did not differ between both groups (p = 1.0).

During treatment: In comparison to the parents of propranolol treated children, more parents from the OCS group had worries about food intake (p = 0.005), about the adverse effects of the oral medication (p = 0.007) and the future of their child (p = 0.001). OCS-parents had less confidence in treatment (p = 0.003) and felt their child was not safe with this drug (p = 0.003). In comparison to parents of children on propranolol, parents with a child on OCS, experienced a more negative influence on father's (p = 0.005) and mother's (p = 0.008) work. Treatment with OCS resulted in restrictions to participate in the national immunization program (p = <0.001). Besides these significant differences between both treatment groups there was a marked tendency to feeling more insecure during treatment and more worried concerning growth and development of the child for the OCS group. There also was a tendency about OCS-treatment being more time-consuming than propranolol treatment. The mean QoL-score for this period was higher for the parents of the propranolol group (p = 0.02).

After treatment: The parents of propranolol group seemed more content with the treatment outcome directly after treatment with a tendency to significance (p = 0.019). The mean Qol-score for treatment outcome directly after treatment seemed to be higher for propranolol parents (p = 0.049). After three months a similar trend was observed (p = 0.03). (Table 4)

Expectations for the future: More parents from the OCS group stated to have become extra concerned about the health of their child (p = 0.004). The mean Qol-score for the period after treatment was higher for the parents of the propranolol group (p = 0.03).

Figure 1a
Patient I-3 in Table 2

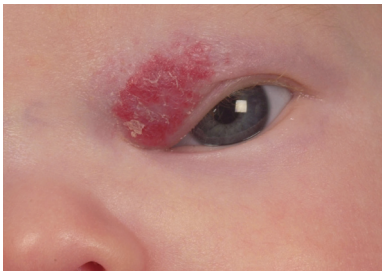

Figure 1b
Patient II-3 in Table 2

Table 2 IH characteristics of 16 matched patients

Pro group	Gender	Location	Clinical subtype	Morphological subtype	Age at start treatment (months)	Duration of treatment (months)	Ulceration
I-1	F	Periocular	Deep	Loc	3.03	7	-
I-2	F	Lip	Sup/Nod	Loc	3.53	11	+
I-3	F	Periocular	Mixed	Loc	3.47	6†	-
I-4	F	Periocular	Deep	Loc	4.40	11	-
I-5	M	Periocular	Deep	Loc	5.20	8	-
I-6	F	Periocular	Sup/Nod	Loc	5.37	14	-
I-7	F	Forehead	Sup/Nod	Loc	3.83	6	+
I-8	M	Periocular	Deep	Loc	2.67	9	-
I-9	F	Cheek	Sup/Nod	Segm	3.30	10	+
I-10	F	Face PHACES	Sup/Mac	Segm	0.67	12	+
I-11	M	Periocular	Sup/Nod	Loc	4.33	7	-
I-12	F	Ear	Sup/Nod	Loc	2.90	11	+
I-13	M	Cheek	Mixed	Segm	2.03	12	+
I-14	F	Lip	Sup/Nod	Segm	2.27	11	+
I-15	M	Periocular	Sup/Nod	Loc	3.43	8	-
I-16	M	Perioral	Sup/Mac	Segm	3.00	10	-

Pro, Propranolol; OCS, Oral corticosteroids; F, female; M, male; Sup/Nod, superficial nodular; Sup/Mac, superficial macular; Loc, local; Segm, segmental; +, present; -, absent

† Patients shown in Figure 1

	OCS group	Gender	Location	Clinical subtype	Morphological subtype	Age at start treatment (months)	Duration of treatment (months)	Ulceration
	II-1	F	Periocular	Mixed	Loc	3.30	12	-
	II-2	F	Lip	Sup/Nod	Loc	3.23	2.5	+
	II-3	M	Periocular	Mixed	Loc	3.70	3.5†	-
	II-4	F	Periocular	Deep	Loc	3.17	6	-
	II-5	F	Periocular	Mixed	Loc	2.40	1	-
	II-6	F	Periocular	Deep	Loc	3.60	8	-
	II-7	M	Forehead	Sup/Nod	Loc	1.97	11	+
	II-8	M	Periocular	Deep	Loc	3.67	2	-
	II-9	F	Cheek	Sup/Nod	Segm	2.33	4.5	-
	II-10	F	Face PHACES	Sup/Mac	Segm	2.17	12	+
	II-11	F	Periocular	Sup/Nod	Loc	2.77	9.5	-
	II-12	F	Cheek	Sup/Nod	Loc	1.67	8	+
	II-13	M	Cheek	Mixed	Segm	1.47	1	-
	II-14	F	Paranasal	Mixed	Segm	3.70	3.5	+
	II-15	F	Periocular	Deep	Loc	3.93	1.5	-
	II-16	F	Perioral	Sup/Mac	Segm	2.77	6	+

Table 3 Mean impact of IH treatment and contentment with treatment outcome scores for parents with IH children treated with propranolol or OCS

	Pro (n=16)	OCS (n=16)	p-value
Prior to treatment: Impact of treatment			
1. I am well informed about my child's treatment	3.37 (0.81)	3.06 (1.12)	0.373
2. I knew what the adverse effects of treatment could be	2.87 (1.46)	2.56 (1.50)	0.555
3. For a while I had doubts about starting treatment	1.44 (1.50)	1.25 (1.29)	0.708
4. I wondered if starting treatment for my child's IH was the right thing to do	2.12 (1.31)	1.56 (1.32)	0.235
5. I wondered how important starting treatment was when I heard IHs are benign	1.00 (1.41)	0.75 (1.00)	0.568
During treatment: Impact of treatment			
6. I felt insecure not knowing what the adverse effects of treatment would be	1.81 (1.52)	2.69 (1.25)	0.085
7. During treatment I felt sometimes insecure	1.94 (1.34)	2.87 (0.62)	0.019
8. I had little confidence in treatment	0.31 (0.48)	0.87 (0.50)	*0.003*
9. I had a feeling that my child would not be safe with this drug	0.50 (0.73)	1.44 (0.89)	*0.003*
10. I had extra worries when my child was ill	1.56 (1.37)	2.56 (1.32)	0.043
11. I had worries about the growth/development of my child	1.19 (1.17)	2.25 (1.18)	0.016
12. I had worries about the nourishment of my child	0.87 (1.15)	2.25 (1.39)	*0.005*
13. I had worries about the adverse effects of this drug	2.00 (1.21)	3.06 (0.77)	*0.007*
14. I had worries about the appearance of my child	1.56 (1.26)	2.44 (1.26)	0.059
15. I had worries about the future of my child	0.94 (1.12)	2.31 (1.01)	*0.001*
16. Treatment took a lot of time (e.g. hospital visitation)	2.31 (1.25)	3.25 (0.58)	0.013
17. Treatment had a negative influence on our daily activities (e.g. going to day-nursery, hobby, sport, relaxation)	1.00 (0.97)	2.06 (1.44)	0.021
18. Treatment had a negative influence on father's work	0.44 (0.51)	1.37 (1.09)	*0.005*
19. Treatment had a negative influence on mother's work	0.69 (1.01)	1.94 (1.44)	*0.008*
20. Treatment had a negative influence on house keeping	0.81 (0.98)	1.31 (1.30)	0.229
21. Treatment was an emotional period for me/us	1.81 (1.33)	2.81 (1.05)	*0.025*
22. Treatment was a burden physically (e.g. lack of sleep, exhaustion)	1.31 (1.3)	2.00 (1.67)	0.205
23. Treatment had a negative influence on the vaccination of our child	0.56 (0.81)	2.44 (1.50)	*<0.001*

Table 3 Continued

	Pro (n=16)	OCS (n=16)	p-value
After treatment: Impact of treatment and contentment with treatment outcome			
Directly after treatment			
24. I am content with treatment outcome	3.75 (0.45)	2.94 (1.18)	0.019
25. I am content with the care program of this hospital	3.44 (0.96)	3.13 (0.89)	0.347
26. Treatment was different from what I expected	0.87 (1.09)	1.50 (1.32)	0.154
Three months after treatment			
27. I am content with treatment outcome	3.81 (0.40)	3.06 (1.18)	0.027
28. I am content with the care program of this hospital	3.44 (0.96)	3.25 (0.86)	0.565
Expectations for the future			
29. I think my child will be content with treatment outcome	3.56 (0.63)	2.56 (1.41)	0.017
30. I am not having any worries about my child's appearance	3.00 (1.03)	2.12 (1.41)	0.055
31. I am having extra worries about the health of my child	0.44 (0.81)	1.62 (1.26)	*0.004*
32. I would choose this treatment again	3.81 (0.40)	2.94 (1.24)	0.015

Scores stated as mean (SD). Pro: Propranolol; OCS: Oral corticosteroids
Significance level of $p < 0.01$
A higher score means more agreement or a higher quality of life

Table 4 Quality of life scores for parents with IH children treated with propranolol or OCS

QoL-score for different periods	Pro (n=16)	OCS (n=16)	p-value
Score prior to treatment	6.00 (1.63)	6.00 (2.31)	1.000
Score during treatment	7.12 (1.93)	5.50 (1.75)	0.018
Score directly after treatment	8.50 (1.10)	7.25 (2.18)	0.049
Score three months after treatment	8.88 (0.89)	7.50 (2.22)	0.029
Score for the future	8.63 (0.81)	7.50 (1.79)	0.032

A higher score means a higher quality of life.
Scores stated as mean (SD). Pro: Propranolol; OCS: Oral corticosteroids
Significance level of $p < 0.05$

Discussion

Before the serendipitous discovery of propranolol in 2008, OCS were the first choice treatment for complicated IHs. In the subsequent period, the adrenergic beta-antagonist propranolol rapidly took over this role. Meanwhile, there have been several studies comparing the effect of both treatment modalities for this indication.[14,21-24] A study comparing the impact and contentment of both treatments has never been performed. These are however interesting aspects of both treatments, particularly for propranolol, a primary cardiac drug without a long reputation in the dermatological field. In the present study, we address impact and contentment of both treatment modalities in children with a cervicofacial IH treated with propranolol or OCS and their parents. Because data on the more favorable effect/side effect profile of propranolol are emerging, [11-13] the option of giving high doses OCS for IHs does not seem ethical anymore. Therefore prospective and blinded studies are impracticable. A case control study design seemed like an adequate alternative. For this study, the best possible matches were made between cervicofacial IH-patients from our cohort treated with propranolol (since September 2008) and OCS (treated before 2008). This method for case control study has been used previously to evaluate the effect of propranolol in ulcerated IH.[16] The search for optimal matching would ideally be based on validated scoring systems like the recently described Hemangioma Severity Scale (HSS) in prospective studies.[25] For this study however, matching based on photo-documentation and medical records was the best possible way, because of the retrospective character of the study design.

Prior to treatment, the two matched treatment groups showed no major differences on the items of our medical information questionnaire. This similarity between both groups prior to treatment supplements the comparability between both groups and gives more value to the outcome of our questionnaire 'during' and 'after' treatment.

During their child's treatment, parents from the OCS group seemed to significantly feel overall more concerned and insecure, compared to the parents of the children treated with propranolol. Additionally, parents from the propranolol group perceived less negative influence on normal life issues, including parents' work and the vaccination of their child, and gave a higher Qol-score for this period. The reason for the greater influence on everyday life (and parents' work) experienced in the OCS group, has not been specifically investigated in this study, but could be explained by more outpatient controls due to the treatment schedule of OCS and the advice not to bring the child to daycare. Also after treatment, the parents of propranolol treated IH patients gave significantly higher Qol-scores than OCS-parents.

Since this retrospective study design inevitably has limitations, conclusions from this study can only be drawn carefully. One limitation of this study may be the fact that children treated with the recently discovered treatment propranolol were younger than the patients in the OCS group at the moment of the interview. So, parents in the

propranolol group may not yet be thinking of possible necessity of subsequent treatment. This age difference and its associated difference in time after completion of treatment may also have influenced the grading of treatment outcome and impact of treatment by the parents by an inevitable recall bias.

Another limitation may be the difference in treatment duration for both groups, this being inextricably linked with the two treatments. Propranolol was continued until the age of 12-18 months; much longer than OCS therapy was given. This may also influence parents' grading.

In addition, the questionnaires used in this study were not validated. But in literature, no validated questionnaires focusing on IH do exist today. To increase however the discriminative power of the questionnaire, the 5 point Likert scale was applied.

Finally, testing all the different items in two comparable matched treatment groups brings the risk of 'multiple testing'. Therefore in this study data were interpreted carefully and a significance level of $\alpha < 0.01$ was used to assess the impact of treatment and contentment with treatment outcome.

Despite these limitations, this is the first study to address differences in impact of treatment and contentment with treatment outcome between children with cervicofacial IHs treated with propranolol or OCS. The results of this study show that propranolol seems to change the impact of IH as a disease, its treatment as well as the quality of life of the parents by reducing additional distress in parents of cervicofacial IH patients. Furthermore, OCS treatment (as opposed to propranolol) also negatively influenced normal issues in the life of young children and families (like vaccination and going to day care while parents were working).

In everyday practice, the awareness of the impact of treatment and contentment with treatment, underline the choice for propranolol in the treatment of function- or life threatening IHs.

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5

Imaging of infantile hemangioma and the future role of three-dimensional stereophotogrammetry

5.1

Three-dimensional stereophotogrammetry: a novel method in volumetric measurement of infantile hemangioma

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Abstract

Accurate and objective measurement of volume changes in infantile hemangiomas (IH) is essential in routine clinical practice and clinical studies, particularly in the changing therapeutic landscape after the discovery of propranolol. Several bedside techniques for volume measurement have been described in literature, but an objective method of measurement of this variable, dynamic vascular tumor is lacking. Three-dimensional (3D) photo-technology with data analysis is an up and coming technique in the objective measurement of facial volume changes. In this pilot study, the usability and clinical relevance of two methods of 3D stereophotogrammetry in the volume measurement of IH were explored.

Introduction

Infantile hemangiomas (IH) are the most common benign tumors of infancy, characterized by rapid growth during the proliferation phase in the first year of life followed by slow regression.[1] The clinical appearance of IH is variable, which makes assessment of growth and regression difficult, especially in voluminous IHs. Therefore, no standard method for measuring IH dynamics during growth and involution exists.

Accurate objective assessment of volume changes in IH is essential in routine clinical practice and clinical studies. Since the discovery of the effectiveness of beta-blockers for IH, there is an increasing need to evaluate and compare therapeutic effects.

In the past few years, three-dimensional (3D) photo-technology has evolved rapidly. Three-dimensional cameras (3D stereophotogrammetry) in combination with specialized software seem useful in assessing objective and quantitative evaluation of volume changes in IH. A number of reproducibility and validity studies of 3D stereophotogrammetry have been performed.[2,3] It can be concluded from earlier studies that surface-based registration is an accurate method of comparing 3D photographs of the same individual at different times.[2]

To the best of our knowledge, no studies have been performed to investigate the relevance of 3D photographs for IHs. The usability and clinical relevance of two methods of 3D stereophotogrammetry for volume quantification in IH were explored in this pilot study.

Patients and Methods

This prospective study sample comprised 11 IH patients who visited our vascular anomalies clinic. Inclusion criteria were: patients with an IH in the head and neck region of the superficial nodular, deep or mixed type, with an indication for propranolol treatment. Three-dimensional photographs of the patients were taken at the start (T0) of propranolol treatment and at the first control visit (T1). A 3D stereophotogrammetric camera setup (3dMDfaceTM System, 3dMD Ltd, Atlanta, USA) was used. The camera setup consisted of two pods, each equipped with three digital cameras and a flash.[4] During acquisition, patients were carefully positioned in a natural head position.[5] A trained photographer took all 3D photographs (Figure 1).

Two methods are described for the 3D measurement of the changes between two different moments in time.

Method 1: Superimposing images

The 3D photographs taken at T0 and T1 were superimposed using the surface based matching tool of the Maxilim® software.[2] In medical imaging, this matching procedure is

Figure 1 Three-dimensional (3D) camera setup and 3D photograph of patient with infantile hemangioma

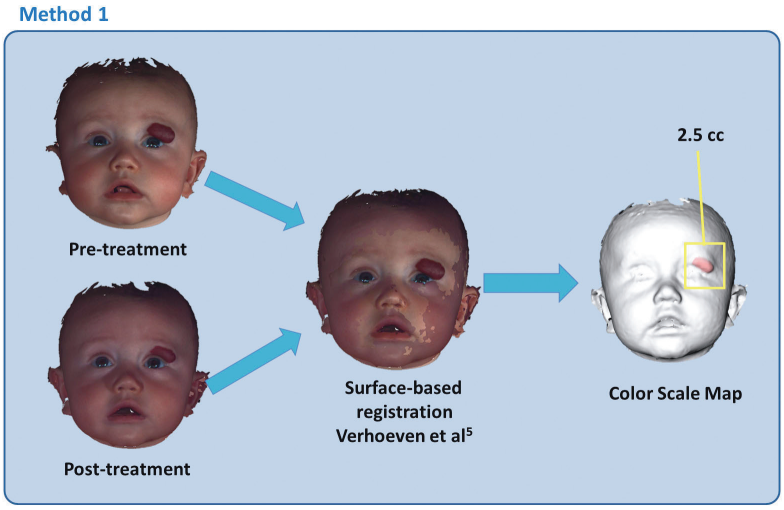

Figure 2 Flowchart method 1: Superimposing images

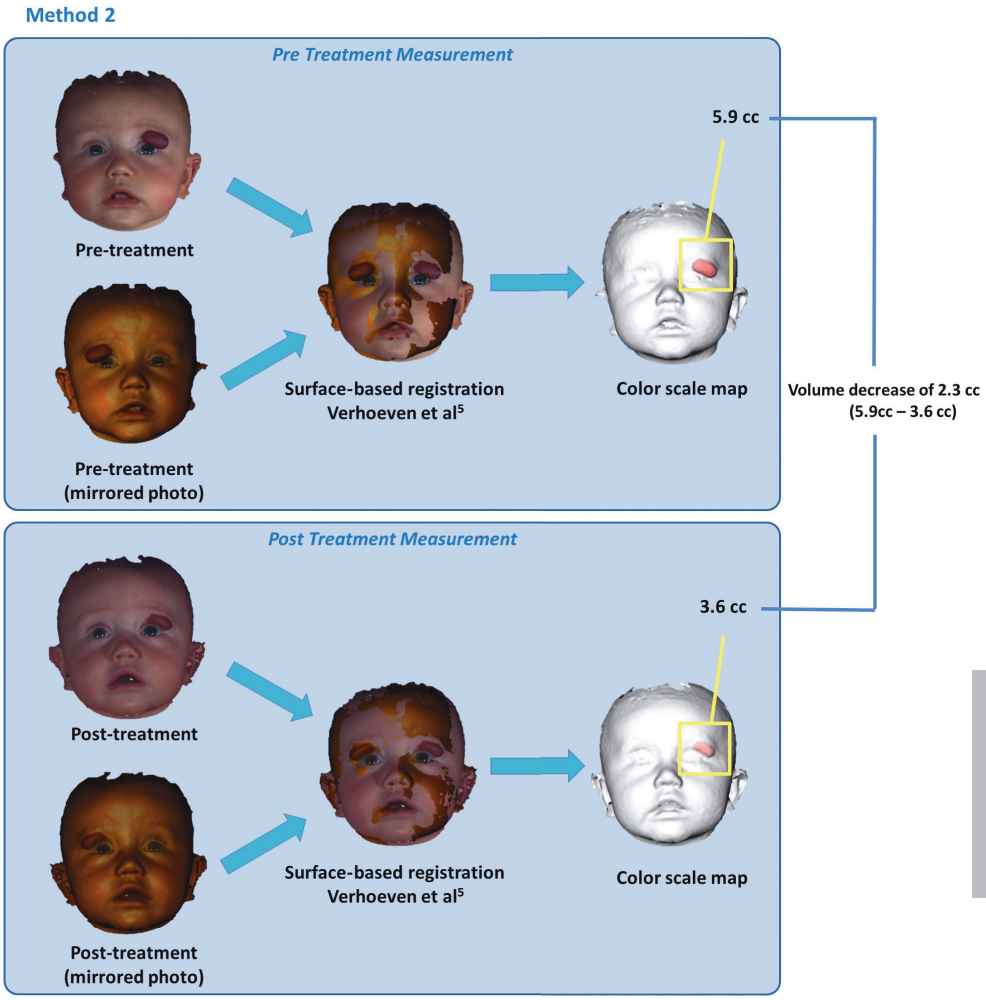

Figure 3 Flowchart method 2: Mirroring images

referred to as *surface-based registration*. After this registration procedure with volume subtraction, a color map (distance map) could be calculated illustrating the volume differences between T0 and T1 as a color scale image, indicating the unchanged areas (in white), decreased volume (in red discoloration) and increased volume (in green discoloration). A higher intensity of discoloration corresponds with a larger change in facial volume. The lighter red areas indicate a small difference (decrease) between the two 3D images, lighter green areas indicate a small increase. Areas with a more intense red or green color indicate a larger decrease or increase, respectively.

From this color map, the region covering the IH (which showed a red discoloration) was selected and the mean difference between the photographs could be calculated (Figure 2).

Method 2: Mirroring images

Surface-based registration was applied in the second method as well, but in another way. The 3D photograph taken at T0 was mirrored and aligned with the original 3D photograph.

The color map was subsequently computed, and the volumetric difference between T0 and T1 could be calculated. This mirroring procedure was validated earlier and described by Verhoeven and colleagues.[6] The procedure was repeated with the 3D photograph taken at T1, resulting in two mean differences and two volumes. By subtracting the post-treatment volumes from the pretreatment volumes a difference could be computed. (Figure 3).

Results

This study included 11 patients (eight girls, mean age 4.3 months at time of first photograph; range 2.0-12.5 months). T0 was the time of the first photograph at the start of propranolol treatment and T1 was the time of the first control visit (mean 9.1 weeks after starting treatment, range 3.1-16.6).

Table 1 Characteristics of IH and time between photographs

Patient number	Sex	Location of IH	Type of IH	Crossing the facial midline	Time between photographs (wk.)
1*	Male	Upper eyelid	Nodular	No	3.1
2	Female	Forehead	Combined	No	6.9
3	Female	Orbital	Deep	No	16.6
4	Female	Nostril	Combined	Yes	3.9
5	Female	Cheek	Deep	Yes	14.6
6	Female	Upper eyelid	Deep	No	10.6
7	Male	Nose tip	Nodular	No	6.9
8	Female	Occiput	Nodular	Yes	13.4
9	Female	Upper eyelid	Nodular	No	8.0
10	Female	Cheek	Deep	No	7.4
11	Male	Upper eyelid	Nodular	No	8.6

* Patient in Figs. 1, 2 and 3.

Table 1 shows the characteristics of the IHs; including location, type and whether or the IH crossed the facial midline. Table 2 illustrates the volume differences measured between T0 and T1 for both methods.

Table 2 Absolute volume differences in cc after propranolol treatment between T1 and T0 in both methods

Patient number	Absolute volume difference cc) Method 1	Absolute volume difference (cc) Method 2
1*	-2.5	-2.3
2	-3.3	-3.3
3	-5.6	-4.4
4	-1.9	not suitable for method 2
5	-4.0	not suitable for method 2
6	-4.9	-4.8
7	-1.6	-1.5
8	-4.2	not suitable for method 2
9	-2.6	-2.6
10	-2.0	-2.8
11	-0.6	-0.6

*Patient in Figs. 1, 2 and 3

Discussion

Infantile hemangiomas have dynamic growth patterns and great clinical variability, complicating volume measurements. In most studies, 2D photographs have been taken to monitor the evolution of the IH, but accurate volumetric measurements cannot be derived from this technique, only overall evaluation and follow-up. To the best of our knowledge only three publications[7-9] have described bedside techniques for estimating IH volume. In addition to the inevitable interobserver variation, these methods model IH as perfect spheres, half-spheres, or ellipsoids, making them moderately suitable for assessment of irregularly shaped IH.

Radiologic diagnostics such as serial duplex ultrasonography may be applicable but are operator dependent. Other imaging techniques such as magnetic resonance imaging and computerized tomography are generally not practical for measuring changes in volume, because of costs, the need for sedation, and the involvement of invasive radiation in serial measurements.

Since 2008, propranolol has been an up and coming, successful treatment option for complicated IHs. After the discovery of this beta-blocker, several associated new therapies

emerged.[10,11] With the advent of these novel therapies, there is an increasing need to evaluate or compare treatment effects and possible regrowth or relapse after cessation of treatment but also to evaluate the course of untreated IH in functionally important threatening areas (e.g. eye, nose). These findings may be important in the considering whether to treat.

Three-dimensional stereophotogrammetry can be useful in daily clinical practice in evaluating facial volume changes, not only with subjective parameters but also with objective measurements. An increasing number of hospitals have acquired this technology. The time involved in image acquisition is limited and is a function of correct positioning of the patient. The time needed to capture high-quality 'external surface' photographs using this technique is < 2 milliseconds, which makes it ideal for collecting 3D data from faces, even in children or babies. Reconstruction of the 3D image takes 30 seconds of computational time and post-processing of the images takes approximately 15 minutes per case. With adapted software, this technique is also applicable to IH at some other sides of the body, but it is most suitable for the head and neck region.

Volumetric registration of IH with two methods of 3D photography was explored in this pilot study. Method 1 is more basic and calculates the difference in the region of interest of two photographs taken at different times. This method can be used for voluminous IH, even for IH crossing the midline of the body. The major drawback of this technique is that the effect of the growth of the child cannot be excluded, although this is inevitable with any technique of volume measurements of tumors occurring in infancy and childhood.

Method 2 is slightly more complicated and uses mirroring of the face to calculate the volumetric difference at two different times. A disadvantage of this method is that it applicable only for unilateral IH and it is based on facial symmetry as baseline. The major advantage is that the effect of growth is minimized. The second method may be more accurate for IH not crossing the midline, especially in the case of longer time intervals between the measuring points. When the times between photographs are closer together, either method may be suitable.

Given the small number of patients enrolled in this pilot study, no statistical calculations were performed to illustrate comparability of the techniques. The focus of the study was the applicability. A larger study with more patients will follow to determine the statistical difference between the techniques more accurately.

Conclusion

Three-dimensional stereophotogrammetry is a promising, new, accurate, fast, noninvasive way to determine and compare volumetric changes in IH.

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6

Further developments from casuistic experience with propranolol

6.1

Propranolol treatment in life-threatening airway hemangiomas: a case series and review of literature

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Abstract

Objective Infantile hemangiomas (IHs) in the airway may be potentially life-threatening during the proliferative phase. Available treatments like oral corticosteroids (OCS) and chemotherapeutic agents usually showed variable responses and serious side effects. Propranolol is a new and promising treatment option.

Methods A case series of five IH patients with airway involvement is presented, supplemented with a review of literature. Propranolol treatment (2.0-3.0 mg/kg/day) was initiated between 3 weeks and 6 months of age. Three cases were treated with propranolol monotherapy, two cases with OCS primarily and propranolol secondarily, in which treatment with OCS could be reduced rapidly.

Results In our case series a dramatic, fast response was observed in all cases, with a permanent effect after discontinuation in four cases. In one patient a relapse of airway problems occurred 2 months after discontinuation of propranolol at 16 months of age; this resolved after re-start of propranolol. Review of literature together with these five cases showed 81 patients with airway IHs treated with propranolol. Propranolol was effective in 90% of the cases and seven patients were classified as non-responders. Eight IHs relapsed while weaning of propranolol or after discontinuation; dose adjustment or restart was effective in most cases but one patient appeared resistant to therapy.

Conclusions Propranolol seems to be a rapidly effective and safe treatment strategy for most IHs obstructing the airway. Because of the fast and important effects of propranolol, randomized controlled trials are hardly justifiable for this specific, relatively rare but, acute treatment indication. Despite the efficacy of propranolol, close monitoring of the patients with an airway IH is required, considering the risk of relapse of symptoms during or after treatment and the reported resistance to propranolol in at least 9% of the published cases. The dose and duration of treatment should be high and long enough to prevent relapse. Further research should focus on the optimal treatment protocol; the actual percentage of non-responders and also the mechanism of resistance to propranolol is unknown and needs to be illuminated.

Introduction

Infantile hemangiomas (IHs) are true neoplastic proliferations of endothelial cells and the most common benign vascular tumors in children. An IH has the characteristic to proliferate rapidly in the first year of life. Most IHs proceed to resolution over a period of months to years without complications, not requiring any medical intervention.[1] The clinical significance of IHs varies widely and is often linked to their location, size and type. The predilection area for IH is the head and neck region; external compression of the airway or airway localization with obstruction may lead to life-threatening situations. Cutaneous signs of airway IHs typically are segmental skin lesions in a mandibular distribution ('beard hemangioma') in up to 50% of the patients. Patients usually present with stridor, respiratory distress or feeding difficulties.[1,2] Airway IHs can be evaluated by nasopharyngoscopy, laryngoscopy and/or magnetic resonance imaging (MRI). Multiple treatment modalities have been proposed in the management of airway IHs to maintain airway patency and to avoid tracheotomy and intensive care admission. Treatment options consisted of intralesional and systemic corticosteroids, chemotherapeutical agents (interferon or vincristine), laser therapy and/or open submucosal resection. Unfortunately, these treatment options have only limited therapeutic benefits with potential side effects and risks.[3,4] Until recently, systemic corticosteroid therapy was considered the first choice treatment in (airway) IHs but this therapy was not successful in many cases and entailed serious side effects like hypertension, growth retardation, Cushing face, and an increased susceptibility to infection.[5]

The effect of the oral beta-blocker propranolol on IH is promising, described as a serendipitous finding by Léauté-Labrèze in 2008.[6] Since then, several (case-) reports have demonstrated the effectiveness of propranolol in the treatment of IH, also in case of airway involvement. Potential modes of actions for propranolol in IH include vasoconstriction, a downregulation of angiogenetic factors like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and an upregulation of apoptosis of capillary endothelial cells.[7] More recently there is growing evidence that the renin-angiotensin system (RAS) plays an important role in the mechanism of action of propranolol for IH.[8,9]

To provide definite evidence for the effect of propranolol on IH, randomized double-blinded controlled studies are most desirable. Nevertheless, case series are very useful to establish the role of new therapeutic agents. Several aspects regarding propranolol treatment for IH with airway involvement however remain to be illuminated: e.g. optimal dosage, duration and timing of therapy, effect on the natural course of IH, monitoring of short and long-term side effects and requirement of other treatment modalities.

We present five children with an airway-compromising IH treated with propranolol and a review of cases with airway IH treated with propranolol published in English literature. Finally, important issues and recommendations for the future will be discussed.

Clinical observations

Case 1

A 2-weeks-old female neonate, born at term, presented a segmental IH, covering the right parieto-occipital skull, ear and neck. An ulceration (2 cm diameter), probably in the aplasia cutis spectrum was already visible at birth (Figure 1a). Further examination revealed a grade II-III/VI high frequent systolic murmur, left parasternal, suspected for a ventricular septal defect (VSD). Oral antibiotics were given for 7 days and wound care was started. In the fourth week of life there was rapid expansion of the IH resulting in an inspiratory stridor and feeding difficulties. After ultrasonography showing a massive IH in the right neck region (right glandula parotis and parapharyngeal), the girl was referred to the intensive care unit of our tertiary centre because of a threatened airway.

Propranolol was started in an increasing schedule to the target dosage of 3.0 mg/kg/day (in 3 doses). The inspiratory stridor disappeared within 24 hours and discoloration of the skin localization of the IH was visible within a few days under stable hemodynamic controls and normal fasting glucose levels.

As part of the work-up for PHACES (Posterior fossa brain malformations, Hemangiomas of the face, Arterial Cerebrovascular abnormalities, Eye abnormalities and Sternal defects) echocardiography was performed; the left ventricle (LV) showed dimension on the 95th percentile and revealed a small VSD. During propranolol treatment however, the LV dimensions normalized. Electrocardiography (ECG), MRI of the head and ophthalmologic evaluation showed no abnormalities.

The IH improved dramatically in the following months (Figure 1b). Propranolol was continued until 15 months of age and tapered in 3 weeks. Two months after discontinuation of propranolol, significant recurrence of swelling was observed with respiratory distress and audible breathing during a viral upper airway infection (Figure 1c). Echocardiography showed LV dimensions on the 95th percentile again. Because of this significant relapse of swelling of the IH with concomitant airway symptoms and increased LV dimensions, propranolol was restarted (2.0 mg/kg/day). The swelling of the lesion and audible breathing disappeared again in a few weeks. The treatment was continued till the end of the patients' second year of life (Figure 1d). Then, the propranolol was tapered and discontinued successfully. The IH remained in regression and the patient is still free of airway symptoms at the age of 3.5 year. Residual lesions characterized by fibrofatty tissnue are clearly visible in the neck.

Case 2

A 2-month-old boy, born at term, was referred to the ear nose and throat (ENT) department because of a progressive inspiratory stridor and threatening respiratory failure. A left-sided subglottic IH was diagnosed by laryngoscopy and oral dexamethason 0.5 mg/kg was started. After he showed some clinical improvement, the patient was sent home. Several

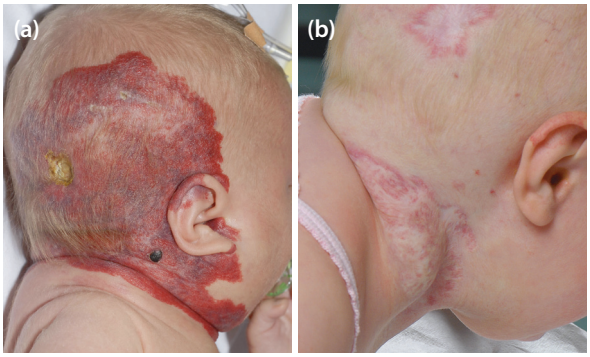
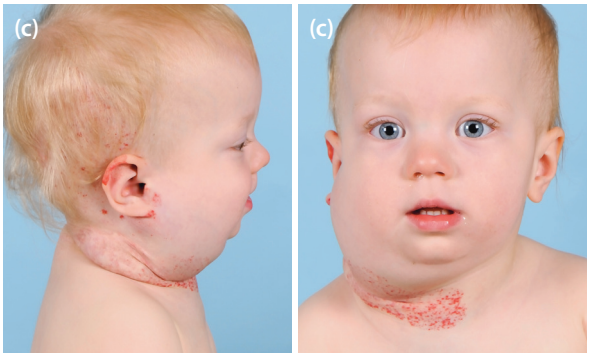
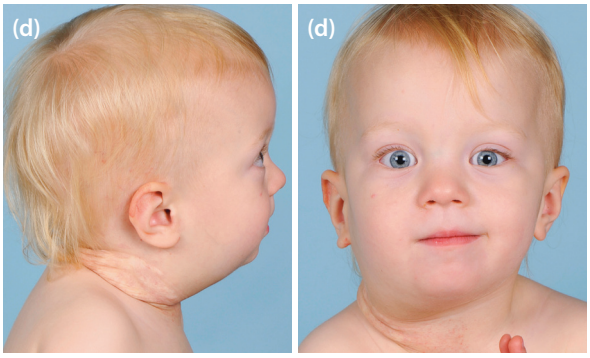


Figure 1
(a) Age 4 weeks; segmental hemangioma with swelling of parotid region. **(b)** Age 9 months; improvement of the hemangioma, 8 months after initiation of propranolol.



(c) Age 18 months; increased redness and swelling, 2 months after discontinuation of propranolol.



(d) Age 22 months; 4 months after restart of propranolol.

readmissions followed because of feeding difficulties and respiratory distress treated with inhalation corticosteroids. After admission to our centre, at the age of 4 months and after cardiac evaluation, propranolol was added at a maximum dose of 2.2 mg/kg/day in 3 doses, resulting in disappearance of the stridor in one day. The respiratory distress resolved completely and the boy no longer presented symptoms of obstructive airway. After initiation of propranolol, the boy was observed clinically for 2 days and the tolerance of propranolol was good with stable blood pressure, heart rate and normal fasting glucose levels. Oral corticosteroids were tapered and stopped successfully in a few weeks' time. Propranolol was continued until the age of 14 months without side effects and tapered over 4 weeks. The patient showed no symptoms of respiratory distress or side effects of propranolol in the 2-years follow-up.

Case 3

A 6-weeks-old boy, born at term, was referred to the department of ENT/ maxillo-facial surgery, because of a left-sided nose obstruction during viral upper airway infections, due to an intracavitar mass, probably an IH. This diagnosis was confirmed with a biopsy revealing a vascular tumor with positive glucose transporter protein 1 (GLUT1)-staining. Because of severe respiratory distress, propranolol was started at the age of 3 months to a target dosage of 2.2 mg/kg/day in 3 doses. General physical examination and cardiological screening (ECG and echocardiogram) before the start of propranolol were normal. Within three days there was a considerable shrinkage of the IH, resulting in disappearance of the nose obstruction, an obvious improvement of the respiration, a more vigorous state and less feeding problems. During propranolol, a viral upper respiratory tract infection resulted in respiratory wheezing and a prolonged expirium. The bronchospasm was attributed to propranolol, the viral infection or the combination of both. Besides, there was a positive family history for asthma. After the propranolol dosage was lowered to 1.5 mg/kg/day and a corticosteroid inhaler was started, wheezing improved and the IH further decreased. At the age of 12 months, propranolol was tapered successfully and the respiratory wheezing disappeared. In the 2-year follow-up, the patient is doing well without signs of nose obstruction.

Case 4

A 1-month-old girl, born at 37 weeks after a twin pregnancy presented with a progressive segmental IH in the right-sided head and neck region. She was referred to the neonatal intensive care unit due to respiratory distress including stridor, tachypnea and feeding difficulties. Laryngoscopy revealed swelling of the arytenoids and epiglottal fold on the right side. As part of the PHACES work up; cardiac evaluation (ECG and echocardiography), ophthalmologic evaluation and cerebral ultrasonography showed no abnormalities.

The patient started with propranolol on an increasing schedule to 2.0 mg/kg/day in 3 doses. The IH softened and the respiratory symptoms and feeding difficulties improved

within days. Because of remaining mild inspiratory stridor during exercise, the dose was successfully increased to a target dosage of 3.0 mg/kg/day with subsequent adjustments of the dose to the body weight of the patient. The propranolol was well tolerated without any side effects. Concomitant with disappearance of the respiratory distress, there was a significant regression of the cutaneous part of the IH. An MRI of the brain was performed with no evidence of posterior fossa malformations and the psychomotor development was within the normal range.

The propranolol was given till 20 months of age and discontinued successfully without rebound swelling and no signs of respiratory distress in the 12 months follow-up. Some erythema of the skin with fibrofatty tissue remains visible.

Case 5

A 2-month-old female neonate, born at term, presented in a district hospital with progressive inspiratory stridor concomitant with mild hypotonia and reduced tendon reflexes. Direct laryngoscopy showed besides mild laryngomalacia no other abnormalities. MRI of the head and spine revealed compression of the myelum at C1 level due to narrowing of the cervical spinal canal. Therefore a dorsal laminectomy was performed to decompress the myelum. After detubation a severe inspiratory stridor with desaturation was present whereupon endotracheal swelling was hypothesized. A re-intubation was carried out and treatment with dexamethasone was given temporarily. Three days later, detubation could be performed successfully and dexamethasone was discontinued. After 10 days (at 3 months of age), the patient was discharged without any stridor. Ten days later however, she was re-admitted with progressive respiratory distress owing to stridor, tachydyspnoea, desaturations and feeding problems. Considering the cervical myelopathy in the past, laryngomalacia with a viral upper airway infection was hypothesized as the main cause of the stridor and treatment with dexamethasone (0.8 mg/kg/day) was restarted. Cessation of the dexamethasone therapy failed because stridor persisted and a dose of 0.15 mg/kg/day of oral steroids were maintained. Nevertheless intermittent stridor persisted in combination with a Cushingoid appearance. At 6 months of age, re-evaluation with laryngobronchoscopy was performed, because of persisting respiratory distress that revealed a large subglottic IH. After cardiac evaluation (ECG and echocardiogram) propranolol was promptly initiated successfully with an increasing schedule to a maximum of 3.0 mg/kg/day in 3 doses. The stridor disappeared within a few days and the patient remained asymptomatic. The dexamethasone was tapered slowly and propranolol monotherapy is continued till the age of 18 months. In the 1-year follow-up the patient is free of respiratory symptoms.

Review of literature

Methods

Eligible studies were identified by searching the electronic literature (PubMed database) for relevant published reports (using the terms: infantile hemangioma, propranolol, airway obstruction, subglottic, head and neck) and by hand searching reference lists of articles on this topic. The search included reports on this topic published since the initial report of propranolol use for the treatment of IH in 2008, until February 2013. Only human studies in the English language were included in the analysis. Articles describing the use of propranolol for complicated IH without further specification about airway involvement were excluded. Data were extracted from the original reports. Analysis was performed on available data. If patients were doubly reported, they were analyzed one time only, unless longer follow-up revealed new information. Patients were qualified as *good responders* to propranolol if the IH showed persistent regression with disappearance of symptoms. *Treatment failure* was defined as none response to treatment or recurrence of symptoms during propranolol at the target dosage, after initial response. *Relapse* was defined as return of airway symptoms once propranolol was stopped or the dosage was decreased.

Results

Table 1 represents characteristics of published cases with IH complicated by compromised airway, treated with propranolol. Data from 85 children, including our five cases, with airway IH who received propranolol treatment are summarized.[4,10-32] Four of the 85 cases are doubly reported. In total, 81 patients are analyzed, in one doubly reported patient (#14) longer follow-up revealed new information.

Eighty percent (65/81) of the children were girls; the mean age at presentation was 2.2 months (ranged from 2 weeks to 6 months). In 96% (78/81) the airway IH was located subglottically, as an isolated entity or as part of IHs located in the head and neck region.

Seventy-seven percent (62/81) of patients received an alternative treatment with OCS, intralesional corticosteroids, vincristine, laser therapy and/or tracheotomy. These other treatments were given before propranolol, as dual therapy or in case of failure of propranolol treatment. Beta-blocker treatment was mostly initiated after full cardiovascular and respiratory review. Median age at start of propranolol was 3.0 months (range 3 weeks to 22 months). The most common propranolol dose was 2 mg/kg/day (ranged from 1 to 3). Data about efficacy were available in all patients, 81% (66/81) of them had a good permanent response without relapse.

Within a few days after the initiation of propranolol treatment, fading and softening of the skin localization of the IH was noticeable. Symptoms such as dyspnea and hemodynamic compromise also regressed. Many patients formerly receiving OCS could be weaned off OCS within a few weeks. In ten percent (8/81), after good initial response, the IH relapsed once the propranolol was decreased or stopped. Restart of propranolol or

dose adjustment to bodyweight afterwards was effective in most cases but failed in one case. Case #36 developed snoring 3 days after stopping propranolol at the age of 10 months and the effect of restart was not described. Cases #14 and #25 demonstrated clinical symptoms again with significant rebound swelling of the IH at endoscopic evaluation after discontinuation of the first course. Reintroduction of propranolol was successful in case #14, but failed in case #25, resistance to beta-blockers was hypothesized. This last patient required two additional endoscopic procedures and ultimately a laryngoplasty.

In case #1 rebound growth with audible breathing was seen when propranolol was tapered at 15 months, restart had however good effect and at the age of 2 years the propranolol was discontinued without symptoms of respiratory distress. Although propranolol was started early in life, significant residual fibrofatty tissue persisted.

Case #54 required a second course of propranolol due to recurrence 2 months after stopping the first course. It was not documented how long the second course was given. Case #80 developed recurrent stridor after 2 months on propranolol and prednisolone. These symptoms subsided after the dose was increased to 3 mg/kg/day. However at the age of 16 months, symptoms reoccurred on a tapering dosage of propranolol (1.5 mg/kg/day) and bronchoscopy confirmed rebound swelling of the subglottic IH. Restart on 2.0 mg/kg/day was however effective. Mahadevan et al. described in two of ten patients, not further specified, recurrence of airway symptoms after 9 months of therapy, which improved after dose adjustment to body weight.

In nine percent (7/81) of the cases, the symptoms of the airway IH remained present and they were considered as non-responders to propranolol therapy. In case #47, the cutaneous IH improved, but the subglottic component continued to proliferate over time on propranolol treatment. Case #55 is classified as non-responder because she did initially not respond to propranolol, once symptoms relapsed after OCS and open surgery she was restarted on propranolol with fairly response.

Summarized, ninety percent of the cases (73/81) with an airway IH turned out to respond to propranolol.

In only seven patients (#3, #15, #54, #56, #64, #83, #85) noticeable side effects of propranolol were mentioned. Two cases had mild gastrointestinal symptoms. In case #15, severe asthmatic symptoms occurred during the first week of treatment. Propranolol could be replaced successfully by another, more selective beta-blocker (acebutolol) with a comparable clinical effect but without severe bronchoconstriction.[15] In case #3, respiratory wheezing and a prolonged expirium developed during a viral upper respiratory tract infection. The propranolol dosage was lowered to 1.5 mg/kg/day and a corticosteroid inhaler was started. This resulted in an improvement of wheezing and nevertheless a steady decrease of the IH. Case #83 appeared to have a low blood pressure associated with impaired peripheral circulation, during a routine clinic visit. The dosage of propranolol was not changed.

Table 1 IH characteristics of 16 matched patients

Author	Pt. no	Gender	Location of IH	Age at presentation (months)	Alternative treatment
Our cases	**1**	F	Right glandula parotis, parapharyngeal	1	None
	2	M	Subglottic	2	Corticosteroids
	3	M	Nose: intracavitar	1.5	None
	4	F	Beard, neck, arytenoids, epiglottic	1	None
	5	F	Subglottic	2	Corticosteroids
Blanchet*	**6**	F	Subglottic	3	Corticosteroids
Buckmiller	**7**	F	Beard, subglottic	2 weeks	Corticosteroids, laser, vincristine
Canadas	**8**	F	Subglottic	2	None, later open surgery
Denoyelle	**9**	F	PHACES, lip, parotid, chest, subglottic	2	Corticosteroids, vincristine
	10	F	Mucosal, subglottic	4	Corticosteroids
Guye	**11**	M	Subglottic	6 weeks	None
Jephson	**12**	F	Subglottic	4	None
Leboulanger	**13=9**[b]	F	Subglottic, PHACES	1.5	Corticosteroids, vincristine
	14=10[b]	F	Subglottic, cutaneous hemangiomas	4	Corticosteroids
	15	All F except one M	Subglottic	3	Corticosteroids
	16		Subglottic, PHACES	1.5	Corticosteroids
	17		Subglottic	3	None
	18		Subglottic	3	Corticosteroids, laser
	19		Subglottic	3	Corticosteroids, laser
	20		Subglottic	2	Corticosteroids, laser
	21		Subglottic	1.5	Corticosteroids
	22		Subglottic	3	None
	23		Subglottic, large facial	3 weeks	None
	24		Subglottic	2	Corticosteroids, laser
	25		Subglottic	1	Corticosteroids, laser
	26		Subglottic	4	Corticosteroids
Maturo and Hartnick	**27**	F	Supraglottic	3	Laser
	28	F	Subglottic	5	None
Mistry	**29**	F	Pharyngeal/subglottic	5 weeks	Corticosteroids

	Age at start of propr. (months)	Propranolol dosage (mg/kg/day)	Duration therapy (months)	Age at end propranolol (months)	Response: good, relapse or failure	Follow up after discontinuation (months)	Reported side effects	Ref
	1	3	1st 14 2nd 7	1st 15 2nd 24	Relapse, restart good effect	18	None	
	4	2.2	10	14	Good	24	None	
	3	2.2	9	12	Good	24	Wheezing	
	1	3	19	20	Good	12	None	
	6	3	12	18	Good	12	None	
	3	3	9	Ongoing	Good		None	4
	22	2	4	Ongoing	Good		None	10
	2	2-3	3	5	Failure		None	11
	11	3	7	18	Good	NA	None	12
	4	2	1	Ongoing	Good		None	
	6 weeks	NA	8	9.5	Good	9	None	13
	4	1 - 2	5	Ongoing	Good		None	14
	11	3	Mean 6	Ongoing	Good		None	15
	4	2	1st 10 2nd NA	1st 14 2nd NA	Relapse, restart good effect	Mean 6 after last endoscopic evaluation	None	
	5	2	1 week	Switched acebutolol	Good		Severe asthma	
	1.5	3	Mean 6	Ongoing	Good		None	
	3	3	5	8	Good		None	
	16	3	Mean 6	Ongoing	Good		None	
	7	2	Mean 6	Ongoing	Good		None	
	5.5	2	Mean 6	Ongoing	Good		None	
	2	2	Mean 6	Ongoing	Good		None	
	3	3	Mean 6	Ongoing	Good		None	
	0.75	3	Mean 6	Ongoing	Good		None	
	8	2	5	13	Good		None	
	2	3	1	3	Relapse, restart propranolol resistant		None	
	4	3	Mean 6	Ongoing	Good		None	
	3	2	6	Ongoing	Good		None	
	5	2	3	Ongoing	Good		None	16
	5 weeks	2	8	Ongoing	Good		None	17

Table 1 Continued

Author	Pt. no	Gender	Location of IH	Age at presentation (months)	Alternative treatment
Rosbe	**30**	F	Subglottic	5 weeks	Corticosteroids, laser, vincristine, tracheotomy
	31	F	Pre-postauricular, neck, subglottic	7 weeks	Corticosteroids
	32	M	Chest, ears, mandibular areas, subglottic	3 weeks	Corticosteroids, dual therapy with propranolol
Sans	**33**	M	Nose with dyspnoe	NA	Corticosteroids
	34	F	Face, parotidal areas, subglottic	NA	Corticosteroids
	35	M	Hemiface, neck, nose, pharynx and glottis.	NA	Corticosteroids
	36	M	Face (nasal tip), mediastinal area	NA	Corticosteroids
Theletsane	**37**	F	Lip, ear, neck, laryngeal, oropharyngeal, subglottic	2 weeks	Corticosteroids
Truong	**38**	F	Subglottic	5	Corticosteroids
Truong	**39**	F	Pharynx, subglottic	1	Corticosteroids, tracheotomy
	40	F	Supraglottic, subglottic,	2	Corticosteroids
	41	F	Subglottic	1	Corticosteroids
	42	F	Subglottic	3	Corticosteroids, laser
	43	F	Supraglottic	3	Corticosteroids
	44	F	Subglottic	1	Corticosteroids, open resection
Raol	**45**	F	Subglottic	1	Corticosteroids
	46	F	Subglottic and left leg	1	Corticosteroids
	47	F	Face, neck, chest beard and subglottic	1	Propranolol, later tracheotomy and oral and intralesional steroids
Goswamy	**48**	F	Subglottic	2.5	Corticosteroids, propranolol
	49	F	Nose tip	3	Corticosteroids, propranolol
	50	M	Parotid, submandibular, subglottic	4	Propranolol, later tracheostomy and corticosteroids

	Age at start of propr. (months)	Propranolol dosage (mg/kg/day)	Duration therapy (months)	Age at end propranolol (months)	Response: good, relapse or failure	Follow up after discontinuation (months)	Reported side effects	Ref
	6	1.8	7	16	Good	NA	None	18
	8	1	10	Ongoing (18, weaning)	Good		None	
	3 weeks	2	4	Ongoing	Good		None	
	4	3	10	14	Good	NA[d]		19
	6	2	8	14	Good			
	2	3	8	10	Good			
	9	2	1st 19 2nd ongoing	1st 10 2nd ongoing	Relapse, effect restart unknown			
	6 weeks	2	6	Ongoing	Good		None	20
	15 weeks	2	5	5	Good	NA	None	21
	18	2	10	28	Good	14	None	22
	6	2	6	12	Good	13	None	
	2	2	6	8	Good	10	None	
	5	2	6	11	Good	8	None	
	22	2	6	28	Good	6	None	
	4	2	5	9	Good	10	None	
	1	3	> 12	Ongoing	Good		none	23
	1	3	11	12	Good	NA	None	
	1	3	> 12	Ongoing	Failure		None	
	3	2	15	Ongoing	Good		None	24
	3	2	5	Ongoing	Good		None	
	4	2	1	5	Failure		None	

Table 1 Continued

Author	Pt. no	Gender	Location of IH	Age at presentation (months)	Alternative treatment
Sierpina	**51**	M	Left bronchus	3 weeks	Corticosteroids, antibiotics bronchodilators, laser
Javia	**52**	F	Laryngotracheal	2	Corticosteroids, surgical
	53	F	Laryngotracheal	5	Corticosteroids,
	54	M	Laryngotracheal	2	Corticosteroids
	55	F	Laryngotracheal	1	Corticosteroids, open surgery, tracheotomy
	56	F	Laryngotracheal	3	None
	57	F	Laryngotracheal	3	Corticosteroids, tracheostomy
	58	F	Laryngotracheal	5	1 day corticosteroids
	59	F	Laryngotracheal	2	1 day corticosteroids
	60	F	Laryngotracheal	2	3 day corticosteroids
	61	M	Laryngotracheal	2	Corticosteroids
	62	F	Laryngotracheal	6	Corticosteroids, planning resection and tracheostomy
	63	M	Laryngotracheal	1	None
Mahadevan [c]	**64**	F	Subglottic	3	Corticosteroids
	65	F	Subglottic, parotid, neck	2	Corticosteroids
	66	M	Subglottic	3	None
	67	F	Subglottic	2	Corticosteroids
	68	M	Subglottic	3.5	Corticosteroids
	69	F	Subglottic, parotid, neck	2	Corticosteroids
	70	F	Subglottic	2.5	None
	71	M	Subglottic	4	None
	72	F	Subglottic	3	Corticosteroids
	73	F	Subglottic, parotid	2	Corticosteroids
Solomon	**74**	F	PHACES; face and neck	25 days	Corticosteroids, vincristine

	Age at start of propr. (months)	Propranolol dosage (mg/kg/day)	Duration therapy (months)	Age at end propranolol (months)	Response: good, relapse or failure	Follow up after discontinuation (months)	Reported side effects	Ref
	1	2	1	2	Failure		None	25
	4	2	10	14	Good	15	None	26
	5	2	4.5	9.5	Good	18	None	
	2	2	1st 10.5 2nd NA	Total 12.5, 1st, 2nd NA	Relapse, restart good effect	29	Constipation	
	2	2	10.5	12.5	Initial failure, after surgery recurrence, propranolol restarted with success.	20	None	
	3	2	11	14	Good	11	Diarrhea	
	7	2	13	20	Failure	27	None	
	5	2	8	13	Good	8	None	
	2	2	10	12	Good	10	None	
	2	2	6	8	Good	6	None	
	2	2 increased to 3 at 6 m.	11	Ongoing	Good		None	
	6	2	11	17	Failure	12	None	
	1	2	10	Ongoing	Good		None	
	3	2	9	12	Good	NA	Hypoglycemia	27
	2	2	11	13	Good	NA	None	
	3	2	10	13	Good	NA	None	
	2	2	10	12	Good	NA	None	
	3.5	2	8	11.5	Good	NA	None	
	2	2	7	9	Good	NA	None	
	2.5	2	6	Ongoing	Good		None	
	4	2	6	Ongoing	Good		None	
	3	2	4	Ongoing	Good		None	
	2	2	6	Ongoing	Good		None	
	About 2.5	2	6	Ongoing	Good		None	28

Table 1 Continued

Author	Pt. no	Gender	Location of IH	Age at presentation (months)	Alternative treatment
Katona	**75**	F	Subglottic, face, arm	1.5	NA
	76	F	Subglottic	3	NA
Loizzi	**77**	F	Subglottic	2	None
Durr	**78=32**[b]	M	PHACES; subglottic	16 days	Corticosteroids,
	79	F	PHACES; subglottic	83 days	None
	80	F	PHACES; subglottic, epiglottis, extended to trachea	19 days	Corticosteroids,
	81=30[b]	F	PHACES; subglottic	47 days	Corticosteroids, vincristine, laser, tracheotomy
	82	F	PHACES; subglottic, extended to pharynx, esophagus	NA	Corticosteroids
Graaf	**83**	F	Subglottic	NA	Intralesional corticosteroids
	84	F	Subglottic	NA	Intralesional corticosteroids
	85	F	Subglottic	NA	Intralesional corticosteroids

F, Female; M, Male; NA, not available. Prop, propranolol, Ref, reference

[a] Blanchet et al. treated two patients with acebutolol [4]

[b] If patients were doubly reported, they were analyzed one time only, unless longer follow-up revealed new information (#14)

[c] Mahadevan et al. described in two of ten patients, which one were not specified, recurrence of airway symptoms after 9 months of therapy, which improved after dose adjustment to body weight [27]

[d] A few adverse effects were noted during propranolol treatment in a cohort of 32 patients with severe infantile hemangiomas, including 4 cases with airway involvement.

Discussion

IHs are usually benign self-limiting tumors of infancy but may become life-threatening in case of airway involvement, causing respiratory insufficiency with a difficult interventional approach due to localization. The lack of an effective and uniform treatment plan for airway IHs makes new treatments necessary. We described five children with threatening

	Age at start of propr. (months)	Propranolol dosage (mg/kg/day)	Duration therapy (months)	Age at end propranolol (months)	Response: good, relapse or failure	Follow up after discontinuation (months)	Reported side effects	Ref
	1,5	2	NA	> 12	Good	15	None	29
	3	2	NA	> 12	Good	15	None	
	2	2	6	Ongoing	Good		None	30
	3 weeks	2	Average 18	NA	Good	Average follow up 35(range, 13-76)	None	31
	83 days	2	Average 18	NA	Good		None	
	19 days	2, increased to 3	1st 17 2nd NA	1st 16 2nd ongoing	Relapse, on lower dose. Increasing dose effective		None	
	6	2	10	16	Good		None	
	NA	2	14	Ongoing	Good		None	
	2.5	1.8	NA	Ongoing	Good		Hypotension, vomiting	32
	6	2	NA	Ongoing	Good		None	
	2	2	NA	On going	Good		Cold extremities	

airway IH that caused severe respiratory distress. They were all treated successfully with oral propranolol, which confirms the efficacy of propranolol for this indication. Several lessons can be drawn from the current experience with our cases in combination with the case series described in literature.

Diagnosis

The correct diagnosis has to be made early. In case #5 prolonged treatments with OCS could have been avoided if the correct diagnosis was made and re-evaluation with laryngoscopy was performed earlier while the stridor persisted. In case of uncertainty, a biopsy can be considered with GLUT1 staining; this confirmed the diagnosis in case #3. If the correct diagnosis is made, delay of treatment with propranolol has to be avoided. Other imaging modalities, such as duplex ultrasonography, MRI, computed tomography (CT) with contrast and laryngoscopy may be useful in confirming the diagnosis.[2] But in a

compromised airway due to IH, any delay before starting propranolol should be avoided. From this it is worth considering starting propranolol right away, in case of unexplained respiratory distress, if IH is a serious part of the differential diagnosis before any further investigation. Progressive and unexplained signs of higher airway obstruction, e.g. inspiratory stridor and dyspnea may point towards an airway IH.

Efficacy

In our opinion, propranolol is the first choice treatment for airway IHs considering its efficacy and relatively mild side effects. In cases #1, #3 and #4 propranolol was the initial and only treatment for the IH. Inspiratory stridor disappeared within 24 hours and discoloration and softening of the skin localization of the IH was visible within a few days. These effects have never been equaled by any other treatment in the past.

Review of literature revealed another 76 cases with propranolol treated airway obstructing IHs. Despite the efficacy of propranolol in the majority of this patients, treatment modalities other than propranolol were still initially started, predominantly OCS (77%). These treatments with OCS were however less successful and only after starting propranolol significant clinical improvement was observed. Besides, propranolol has less significant side effects than OCS.[33]

Peridis et al. performed a meta-analysis, on the effectiveness of propranolol for the treatment of airway IHs, compromising 36 patients.[34] In a retrospective manner, they analyzed the effectiveness of propranolol versus steroids, CO_2 laser or vincristine in predominantly case reports with relatively small sample sizes in each treatment group. It could be demonstrated that propranolol is the most effective treatment as compared to former treatments. An important issue is that the patients treated with vincristine and CO_2 laser concomitantly received corticosteroids, which confounded the efficacy assessment of one single treatment. In the present overview of 81 cases the overall efficacy of propranolol appeared to be 90%, including the cases that responded well to a second course of propranolol after unsuccessful tapering of the first propranolol course. Such an effective and safe treatment makes randomized controlled trials hardly justifiable for this specific, relatively rare and severe, acute treatment indication.

Dosage

The most effective propranolol dosage for airway IH treatment has not yet been illuminated. A dosage of 2.0-3.0 mg/kg/day is regularly adequate to reduce the IH mass and to relief respiratory distress. A multi-institutional and multidisciplinary consensus group recommends, for any type of IH, a target dose of 1.0 to 3.0 mg/kg per day with most members advocating 2.0 mg/kg per day, the median dose reported in literature.[35]

Case #3 showed that a lower dosage appeared to be effective as well. Case #4, however, illustrated that a dosage lower than 3.0 mg/kg/day was inadequate in controlling the evolution of the segmental IH in the first months of treatment. Therefore, if well

tolerated, a higher dosage should be tried in case of persistence of symptoms in life-threatening airway IH, considering potential dramatic complications of airway obstruction and unattractive therapeutic options. Propranolol has been used in pediatric patients for the treatment of hypertrophic cardiomyopathy in much higher doses.[36]

Relapse and treatment failure

Most case series provide the short-term effect of propranolol treatment. Many cases (n=38) were already published while still on propranolol treatment lacking long-term data. At least, in eight cases (10%), after good initial response the IH relapsed once the propranolol was tapered or stopped.

Early discontinuation of propranolol, during the proliferative phase, increased the chance of recurrence, illustrated by case #25. Cases #1 and # 80 however showed that relapse of swelling of the segmental IH with a deep component and/or subglottic localization could also occur beyond that phase (after treatment for 15 months). In airway IH we advise to adjust the dose to the bodyweight during the proliferative phase and to continue the propranolol treatment at least until the age of 15-18 months or even longer. Consideration should be given to gradual tapering of propranolol over 2-3 weeks because of the risk of cardiac hyperactivity.

Despite this highly effective treatment, close monitoring of the patient with airway IHs is required considering the risk of relapse of symptoms during or after treatment and the unresponsiveness to propranolol in 9% of the cases. This percentage may be higher due to negative publication bias, so the exact number of non-responders to propranolol needs to be illuminated. However, this percentage of 9% is evidently higher than the reported failure rate of 1.6% for propranolol treatment for any type of IH, in the recent multidisciplinary and multi-institutional consensus paper.[35] There are a number of possible explanations for this difference. Firstly, for some failure-cases it is unknown whether the suggested diagnosis of IH was right. Secondly the failure-rate in the consensus paper may be underestimated because treatment failures may not always be reported.[35] In the last place, one could speculate that the efficacy of propranolol might differ for different types of IH; making further research necessary.

Safety and side effects

After more than 40 years of clinical use of propranolol in infants for cardiac reasons (hypertension, dysrhythmias and hypertrophic cardiomyopathy), there are anecdotal reports of life-threatening complications in the setting of intravenous administration and propranolol overdose.[37,38]

The most commonly encountered side effects of this non-selective beta-blocker are relatively mild; gastrointestinal discomforts, lethargy, sleep disturbances, restlessness, diarrhea and decreased appetite. The potentially more serious complications are (symptomatic) hypotension, bradycardia and bronchoconstriction. The overall frequency

of any complication recorded is about 15% of total 1175 published cases with IH treated with propranolol. In our review of airway IH, in only four patients (4.8%) a noticeable side effect of propranolol was reported. Two cases had mild gastrointestinal symptoms and two had pulmonary symptoms.

In case #3, the patient was started on a regular dose 2.2 mg/kg/day and developed wheezing during viral upper airway tract infection. This bronchospasm may be caused either by propranolol or may be related to the viral infection and disappeared completely after weaning the propranolol. In case #15, severe asthma occurred during the first week of treatment. Propranolol could be successfully substituted by another, selective beta-blocker.[15] These observations emphasize the importance of cardiovascular and respiratory evaluation prior to initiation and during therapy. Considering the potential life-threatening complication of airway IH, initiation of therapy in an inpatient setting for children at risk is essential.

PHACES

In cases #1 and #4 there was a segmental IH in the neck region with suspicion of PHACES syndrome. Although the majority of IHs occurs in otherwise healthy infants, large, segmental facial IHs are possibly associated with PHACES syndrome.[39,40] When PHACES syndrome is suspected, a full workup including complete physical exam and careful cardiac, ophthalmologic, neurologic assessment and imaging is indicated.

Propranolol can be given to the majority of the patients with a congenital heart defect. In case #1, the LV dimensions were increased, secondary to the relatively large shunt of the extended IH. The LV dimension normalized after regression of the IH after propranolol treatment. Whether it is fully safe to treat PHACES patients with beta-blockers is unknown, because of vasculature abnormalities of the brain vessels. Brain perfusion SPECT (Single Photon Emission Computed Tomography) in seven patients however showed significant improvement of symptoms in patients with PHACES treated with propranolol, without signs of a reduction of brain blood perfusion.[41] Additional research is needed to further elucidate this.

Conclusion

Propranolol seems to be a rapidly effective and safe treatment strategy for most IHs obstructing the airway. The exact number of non-responders due to publication bias and the mechanism of resistance to propranolol are however largely unknown and need to be illuminated. Propranolol has many advantages in (airway) IH over other established treatments, such as being non-invasive, having a rapid effect and avoiding prolonged OCS therapy, tracheotomy or prolonged periods of intensive care admission with intubation. Moreover it has a low complication rate and is inexpensive.

Most case series provide the short-term effect of propranolol treatment. This report however has a more prolonged follow-up and focuses on the fact that propranolol should not be discontinued too early, in order to avoid rebound of symptoms due to swelling.

Ideally randomized controlled trials have to be performed to evaluate this new therapy; however given the fast and important effect of propranolol, randomized controlled trials (RCTs) are hardly justifiable for this specific subgroup of IH with an acute treatment indication due to airway obstruction. Therefore case series, preferably in one single large institution, are still very useful to establish the role of new therapeutic agents with respect to historical management of life-threatening IH.

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6.2

Kaposiform hemangioendothelioma with Kasabach-Merritt syndrome: a new indication for propranolol treatment

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Summary

Kaposiform hemangioendothelioma is a rare vascular tumor in children. Especially, in association with the Kasabach-Merritt phenomenon it can be life threatening. The management of these patients is very difficult and an aggressive treatment regime is required. Several multimodality and chemotherapeutic regimens have been described but with variable success and many side effects. We present a 6-week-old boy with Kaposiform hemangioendothelioma and Kasabach-Merritt phenomenon. Ongoing propranolol treatment with only 4 initial courses of vincristine resulted in a remission that lasted at least 1 year.

Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive vascular tumor that mainly occurs during childhood. Clinically, it develops as a violaceous indurated lesion and shows only little tendency to involute spontaneously.[1] KHE has a high mortality rate of 30%, nearly always related to locally invasive effects, visceral inoperable location, or as a result of the Kasabach-Merritt phenomenon (KMP).[2] KMP, first described in 1940, comprises the combination of a KHE or tufted angioma with consumptive coagulopathy[3,4] The primary process behind KMP is platelet trapping within the tumor, with a significant decrease in platelet count (<100 x 10^3/μL). A proposed mechanism for this process is the adhesion of platelets to the endothelium, with the aggregation and activation of platelets.[5] In symptomatic KHE, associated with KMP, aggressive treatment is indicated. However, controlled trials are almost impossible because of the relative rarity of the syndrome. Several treatment combinations have been described with variable success. Vincristine is a therapeutic option but usually an average of 22 weekly courses is needed to induce regression.[6] Propranolol is a new promising treatment option for vascular tumors such as infantile hemangiomas.[7] Other vascular tumors are queuing up for a trial with propranolol. We report a case with KHE and KMP in which propranolol was combined with only 4 initial courses of vincristine, resulting in a strong and lasting response. Possibly, this is the start of a hopeful new approach in this severe, life-threatening condition.

Case report

A 6-week-old boy was admitted to our hospital because of a progressive violaceous, indurated large cutaneous lesion on his abdomen, first noticed at birth and progressed toward his back, breast, and scrotum (Figure 1). General physical examination showed no other abnormalities.

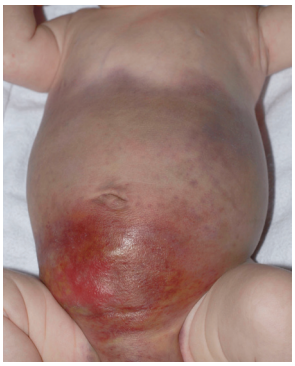

Figure 1
Age 7 weeks, just before treatment with propranolol and vincristine.

Laboratory evaluations showed a hemoglobin level of 6.6 g/dL and severe thrombocytopenia (<10 x 10^3/μL). Furthermore, a coagulopathy was seen with a fibrinogen level of 1.33 g/L (reference range, 2.70 ± 2.44 g/L) and a D-dimer plasma level of 32.3 mg/L (normal <2 mg/L). Echographic imaging of the lesion showed a variable echogenic aspect, presumably in the abdominal wall. Magnetic resonance imaging showed vascular malformation of the entire abdominal wall, especially of the lower abdomen and inguinal region. Histopathologic investigation of the lesion showed areas of endothelial proliferation nodules and some slit-like lumina containing erythrocytes reaching from the dermis to the subcutis. Skin and tumor biopsies were taken after the treatment had already been initiated in a phase of improving platelet counts, because of the otherwise high risk of bleeding. Histopathology of this vascular tumor combined with coagulopathy resulted in the clinical diagnosis of KMP.

Before the start of propranolol, a cardiologic screening (echocardiography and electrocardiogram) showed no abnormalities. The dose was increased to 2 mg/kg/day in 3 doses with monitoring of blood pressure, heart rate, and fasting glucose levels. On the first day of monotherapy with propranolol, the lesion became softer. On account of the low platelet count, our multidisciplinary group could not justify monotherapy with experimental propranolol anymore. Therefore, after mature consideration, vincristine was started in addition to propranolol on the second day. A total of 4 doses of vincristine were administered (67% of 1.5 mg/m^2/wk, once a week) and propranolol was continued. In 10 days, a normalization of the platelet count (239 x 10^3/μL) and an ongoing dramatically clinical decrease of the lesion were seen.

After 4 weeks (Figure 2), vincristine courses were discontinued and propranolol was continued at a dose of 2 mg/kg/day in 3 doses until today. At the age of 15 months, the propranolol dosage was reduced over 2 weeks and then stopped. Neither regrowth of

Figure 2
Age 11 weeks, 4 weeks after starting treatment with propranolol and vincristine.

the tumor nor hematologic abnormalities has been observed until now, at the age of 17 months. The hematologic parameters are being monitored at regular intervals to detect any late relapses of KHE (Figure 3).

Figure 3
Age 10 months, during propranolol monotherapy.

Discussion

KHE with KMP is a potentially life-threatening vascular abnormality that requires aggressive treatment. Complete surgical removal with a large margin has the best reported outcome but is frequently impossible because of the risk of bleeding, extensiveness, and the anatomic site of the lesion.[8] Therefore, other different treatments (or combinations) have been described. Ticlopidine in combination with aspirin, heparin, low molecular weight heparin, embolization, and radiation therapy has been described with variable outcome and limited success.[8–12] Systemic steroids and interferon-α are suggested but with marginal success rates of respectively, 10% and 50% to 60%, with a significant risk of neurotoxicity because of interferon.[2] Currently, vincristine is mainly used for patients with KHE often combined with corticosteroids.[13] Finally, several case reports have been described with positive results of other chemotherapeutic regimens with serious possible side effects.[5,6,14–19]

The nonselective β-blocker propranolol was first described in 2008 by Léauté-Labrèze et al.[20] as a promising and unequaled new therapeutic approach for infantile hemangiomas. The exact mechanism of action is unclear, but vasoconstriction, downregulation of angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor, and upregulation of apoptosis of capillary endothelial cells may be responsible for the outstanding therapeutic effect. In the literature, there are no reports of propranolol in KHE and/or KMP thus far. This may be because of the relatively short experience with propranolol in the treatment of hemangiomas and the rarity of the KMP. But the mode of action that is hypothesized in infantile hemangiomas may be comparable in other vascular

tumors such as KHE. In this case, monotherapy with propranolol could not be justified because of the life-threatening hematologic parameters. Therefore, vincristine was added. Although in the literature, the average treatment duration of vincristine is 22 weekly courses,[6] in our patient a treatment period of only 4 weeks was necessary.

The potential side effects of vincristine are tough: irritability, peripheral neuropathy, and abdominal pain with loss of appetite. Propranolol has long been used for other pediatric indications and has a well-documented safety and side effect profile. Potential side effects include bradycardia, hypotension, hypoglycemia, rash, fatigue, and bronchospasm.[20] No side effects were observed in our patient.

This preliminary report is important as propranolol is safe and seems to have a non-negligible potential effect in KMP. Propranolol seems to be an important addition to the suboptimal therapeutic arsenal for the life-threatening condition of KHE with KMP. The question remains whether the effect of propranolol was solely on the underlying KHE (with a secondary beneficial effect on KMP) or probably on both aspects of the condition.

Obviously, more experience with propranolol in the treatment of KHE is necessary; however, the extraordinary effects in this case need to be communicated in this phase and propranolol should be considered in the treatment for future patients with KHE.

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7

General discussion

7.1 General discussion

In this chapter, firstly the main conclusions of the current thesis will be outlined and discussed in line with the aims formulated in chapter 1. Secondly, the implications of these findings for general clinical practice are described. Finally, new developments and directions for future research will be outlined in the paragraph 'future perspectives'.

7.1.1 Aims of the thesis

Aim 1: To explore the indication area and treatment regimen of propranolol in infantile hemangioma.

After the serendipitously observed, favorable effect of propranolol on IH[1], the Hecovan-working group of RUNMC also started to administer this new treatment option. From September 2008 till now, over 200 patients with complicated IHs were treated with propranolol. Our experiences with the first treated 174 patients from September 2008 till January 2012 were outlined in a prospective way in ***Chapter 2.***

For 173 of the 174 patients (99.4%) treatment could be classified as successful within 3 weeks, defined by fading and softening of the tumor. The patient who did not respond well was a premature newborn (30 weeks of gestation), started at the age of 6.5 months, whose propranolol dose had to be tapered and eventually discontinued due to side effects. This case was however one of the first children treated in our centre. With our increasing experience, we might currently have chosen to further reduce the dosage and continue treatment with intensive monitoring of vital functions. In the other patients with serious side effects, (temporary) dosage reduction made successful continuation of treatment possible. In contrast, in a few other patients, it was decided to adjust the dose upwards to generate an extra therapeutic effect. It can therefore be concluded that some *flexibility* with respect to the dosages may be necessary in order to achieve the optimal therapeutic result with minimal side effects.

Also, with regard to treatment duration, some degree of flexibility is obligatory in order to accomplish the required treatment result. Dependent on the IH subtype and treatment indication, the treatment duration has to be adapted. In general, treatment has to be continued until the end of the proliferation phase, for deep or mixed IHs this implies till the age of 12-16 months. In case of ulceration the treatment duration could be shortened (up to 9-12 months of age), because of the marginal risk of recurrence of ulceration afterwards. For deep periorbital IHs and airway IHs on the other hand, treatment is required till the age of 15-18 months, given the seriousness of complications in case of rebound swelling.

With respect to safety; for 108 of the 174 patients (62.1%) side effects were recorded during treatment. Despite this relative large number, the adverse effects were in general mild, reversible and dose-dependent. Nocturnal restlessness, cold acra, daytime

somnolence and wheezing during upper respiratory tract infections were most commonly reported. In literature, hypoglycemia is the side effect of most concern, impact of this side effect may be aggravated by the fact that propranolol can mask the early clinical symptoms. Therefore, in patients with a high-risk profile for hypoglycemia (patients younger than 3 months, ex-prematures, periods of decreased food-intake or concomitant treatment with OCS), intensive and frequent monitoring was performed, as well as good instructions for their parents. In our patient group, the measured fasting glucose levels were normal and no hypoglycemic side events were observed.

For the majority of the patients, treatment was started in a clinical setting. With our growing experience, treatment was initiated in an outpatient setting for a selected uncomplicated patient group: patients born at term, with normal birth weight, no abnormalities in physical examination, normal blood pressure and electrocardiography and without threatening symptoms. We started the lowest dosage at home and subsequently, the dose was increased to the target dosage during a daycare admission, monitoring heart rate and blood pressure. Important advantages of this treatment schedule were the quick and easy application of the treatment without any time delay due to limited clinical capacity, and the fact that it is more cost-effectively and patient friendly. The potential disadvantage is the absence of monitoring of blood pressure and heart rate after the first low propranolol doses. Due to the pharmacological characteristics of oral propranolol the peak effect on blood pressure and heart rate is one to three hours after administration, also after the first lowest dose. Limited reports are available on accurate data of cardiovascular parameters after initiation of propranolol. Asymptomatic blood pressure drops (diastolic blood pressure below 50th percentile) have been reported in low-risk children.[2,3] Except for one patient, these blood pressures were however for children with normal cardiac function still in the normal range. Standardization of blood pressure measurement and criteria to define hypotension (blood pressure below 5th percentile and/or symptoms) are necessary to assess the relevance of this potential side effect. In a recent report based on a multidisciplinary and multi-institutional consensus conference, cardiovascular monitoring is advised during daycare admissions, 1 and 2 hours after the initial dose and after significant dose increase (>0.5 mg/kg/day), for uncomplicated patients. In addition, at least 1 measurement of blood pressure and heart rate after the target dosage has been suggested.[4] These recommendations are also in line with the Dutch guidelines for the pediatric use of propranolol described in the Dutch Pediatric Formulary (www.kinderformularium.nl). For high risk children the initiation is still necessary in a clinical setting. This approach is actually preferred by the Hecovan-working group, however at this moment treatment is started clinically for logistic reasons. Nevertheless, although propranolol appears relatively safe, considering the potential side effects, a careful assessment should take place before initiating therapy.

In general, from our extensive clinical experience it can be concluded at this moment that propranolol is an effective and safe treatment modality in almost all patients with a

complicated IH. With growing experience, treatment protocols will become clearer although tailor-made adjustments will remain necessary for the individual patient. In addition, with longer follow-up, data about long term safety will become apparent.

Aim 2: To get more insight in the role of propranolol in the treatment of ulceration, the most common complication of infantile hemangioma.

Ulceration is one of the most common and distressing complications in IH. Although relatively common, little is known about the underlying mechanism(s). In ***Chapter 3***, two studies are presented that provide more insight into this problem area, respectively by describing the difference between ulcerated and non-ulcerated IHs and exploring the role of propranolol for this indication.

In the first study, a retrospective analysis was performed of the 465 IH patients visiting the RUNMC from 1997 till 2007. Ulceration was registered in 23% of the patients and the average ulceration time was 8 weeks.

Characteristics of ulcerated and non-ulcerated IHs and the differences between both groups were described. In general larger IHs with a superficial component in areas more predisposed for contamination are particularly at risk for ulceration. A higher incidence of ulceration was found in the IHs localized in the head and neck region but also a significantly high percentage in the diaper area. Taken together, *epidermal involvement* and *susceptibility to trauma and maceration* seem to play a role in pathogenesis. The phase in which ulceration most frequently occurred was during the proliferation phase of the IH. The possible explanation for this observation is that the fast growing IH *outreaches its own blood supply*, resulting in central skin necrosis.[5]

In addition, patients with ulcerated IHs were significantly more often prematurely born infants.

In summary, studying this specific patient group enlarges our insight in the complex multifactorial pathogenesis of ulceration in IH, with a key role for: epidermal involvement, susceptibility to trauma and maceration and finally, necrosis due to outgrowth of blood supply in fast-growing, bulky IHs. This knowledge can be utilized to estimate the potential risk of ulceration, providing arguments for whether or not to start treatment early in order to stop growth of the IH and prevent ulceration.

With regard to the treatment of ulcerated IHs, in literature there is no actual, uniformly accepted therapeutic approach. This is partly the result of the unclear pathogenesis of ulceration, but also due to the highly variable course of the IH and associated ulceration. A generally accepted treatment-triad for ulcerated IHs is: (1) adequate pain management, (2) topical and oral antibiotics and (3) wound care; this in addition to a formerly applied treatment to accelerate the involution of IH (e.g. corticosteroids). This approach regularly had unsatisfactory results. Therefore, the role of propranolol for this complex patient group was explored, in the second part of chapter 3.

Twenty patients with an ulcerated IH treated with propranolol, were matched and compared with twenty comparable patients with a similarly severe ulcerated IH treated before the propranolol era, in a retrospective way. It could be concluded that patients treated with propranolol had a significantly *shorter ulceration time* than the patients in the historical matched control group (8.7 vs. 22.4 weeks). The moment of treatment-start turned out to be relevant as well: *initiation of propranolol earlier in the proliferation phase* nearly always resulted in a shorter ulceration time. In the view of the risk profile for ulceration outlined in the first part of chapter 3, it is probably the best choice to start propranolol early in IH patients with these specific characteristics. Additionally, in case of doubt concerning propranolol start, control visits should be planned regularly during the growth phase of the IH. Although belated initiation of propranolol, particularly after the growth phase of the IH, seems less effective, it is still worth starting in most cases, merely to accelerate involution of the IH.

The observed value of propranolol in case of ulceration should be discussed in light of the limitations of this study. The retrospective, observational character of the study, implicates the risk of confounding. Only randomized placebo-controlled trials would provide the strongest evidence for the effectiveness of propranolol for ulceration in IH. But the generally undoubted clinical efficacy of propranolol in treating IH, makes this type of study almost unethical. Clinically useful conclusions can however be drawn despite the limitations of this study design. We propose that propranolol should be the first choice treatment for seriously ulcerating IHs. It is however preferred to start early in the proliferation phase to increase the effectiveness and prevent these potentially serious consequences, wherever possible.

Aim 3: To enlarge knowledge about quality of life aspects in patients with infantile hemangioma and their families, especially with respect to different treatment modalities.

In recent years there have been several studies comparing the effect of propranolol and OCS in the treatment of IH. The impact of treatment and contentment with treatment outcome however had never been studied and are therefore described in ***Chapter 4***. In this study, the impact of both treatments on daily family life of IH patients and the QoL during and after this period were compared, as well as the parents' contentment with treatment-outcome. The study-design was comparable to the approach used in the second part of chapter 3; the best possible match between 16 patients with a cervicofacial IH treated with propranolol and 16 patients treated with OCS was sought. The data about impact and contentment were obtained using telephone questionnaires. Comparison of the answers of the parents of both patient groups, revealed that during their child's treatment, parents from the OCS group seemed to feel significantly *more worried and insecure*, compared to the parents of the children treated with propranolol. Additionally, parents from the propranolol group perceived *less negative influence on normal life issues*,

including parents' work, day care admission and the vaccination of their child, and gave a *higher Qol-mark for both the period during and after treatment*.

Despite the inevitable limitations of this retrospective study design, it is the first study to address important differences in impact of treatment and contentment with treatment outcome between children with cervicofacial IHs treated with propranolol versus OCS. The results of this study show that propranolol seems to change the impact of IH as a condition, its treatment, as well as the quality of life of the parents. Propranolol treatment reduces concern in parents during the therapy, which also results in greater satisfaction compared to the former approach with OCS. When efficacy and safety will eventually be further established in controlled trials including long term follow-up, the data from the present study may contribute in expanding the indications for propranolol from function-threatening IHs to cosmetically disturbing and quality-of-life-changing IHs.

Aim 4: To explore the future role of quantitative imaging analysis, in particular 3D stereo-photogrammetry in the follow-up of infantile hemangioma growth and regression.

After the discovery of propranolol for the treatment of IH in 2008, several new therapeutic agents emerged that operate in the same pathway that is derived from the concept of beta-blockade as therapeutic target for IH. With these developments, it is important to be able to quantify and compare the therapeutic effects of these novel treatments. Further, there is an increasing need to monitor the natural history of IH (proliferation or involution), which is important in deciding whether or not to intervene. A rapid, non-invasive and accurate technique in volume measurement of IH is however missing. In literature, two-dimensional photography has usually been used to illustrate and monitor the natural evolution of IH as well as treatment effects. This technique can however only be used for overall follow-up and is not suitable for accurate volume measurement. In addition, several bedside techniques for estimating IH-volume have been described.[6-8] These methods entail an inter-observer variation and are not applicable to irregular shaped IHs. Imaging techniques like duplex ultrasonography have been used but with a significant inter-observer variation; CT and MRI are generally not practical because of costs, required sedation and the involvement of invasive radiation in serial measurements for CT-scans.

In recent years, 3D stereophotogrammetry has become an increasingly important technique in evaluating facial surface geometry. In a pilot study, compromising 11 patients, the applicability of this technique for the measurement of volume changes in facial IHs is explored and described in ***Chapter 5***.

To obtain the data from the facial IHs, *surface-based registration* was used, a registration procedure characterized by volume subtraction of digitalized photographs at different times. Two methods of 3D stereophotogrammetry were applied and compared.

Method 1 (superimposing images) is the most basic method and calculates the volume difference of the region of interest of two photographs taken in time. This method is

applicable for every IH with volume. The major drawback of this technique is, that the effect of growth of the face cannot be excluded. This is however inevitable in any other technique of volume measurements of tumors occurring in infancy and childhood.

Method 2 (mirroring images) uses mirroring of the face to calculate the volumetric difference at two different times. The disadvantages of this method are that it is slightly more laborious compared to method 1, only applicable for IHs not crossing the midline and based on facial symmetry as baseline. The major advantage is that the effect of growth can be minimized, making this method very accurate in follow-up volume measurement.

In general, it can be concluded that 3D stereophotogrammetry is a new promising, non-invasive and accurate method in volume measurement of IH. It is expected that if the measuring points are closer together in time, both methods may be suitable and accurate, but method 1 is more basic and generally applicable. In case of long time-intervals between the different measuring points, the second method is more suitable. More extensive studies are needed to specify the usability of both methods for IH.

Aim 5: To investigate and describe the broader applicability of propranolol in vascular tumors.

Since the serendipitous discovery of the beneficial effect of propranolol on the natural history of IH, the indication area of this beta-blocker is increasing. The favorable experience in our centre with propranolol in the treatment of *airway IHs* and *Kaposiform hemangioendothelioma* is outlined in the first and second part of ***Chapter 6*** respectively.

Infantile hemangioma is the most common benign tumor of the head and neck in the pediatric population but if located in the airway, it may evolve into a potentially life-threatening entity. A clinical sign for airway involvement may be a cutaneous IH in the submandibulair region ('beard IH'), but airway IHs can also occur without cutaneous signs. The primary presenting symptom is usually a biphasic stridor, which gets worse when the tumor increases in size, but also respiratory distress and feeding difficulties can be recognized. The mortality rate of untreated symptomatic subglottic IHs is nearly 50%, making early and adequate intervention of vital importance.[9] Until recently, the management of airway IHs could be divided in medical and surgical therapies, often a combination of both therapies was required. Established surgical techniques were endoscopic laser excision, transcervical open excision and tracheotomy for relief of obstruction. Medical options were OCS as first choice treatment, intralesional corticosteroid injection and chemotherapeutic agents like vincristine and interferon as second-line considerations in severe, corticosteroid resistant cases.[10]

Our experience with propranolol treatment of five patients with a life-threatening airway IH is described, together with an overview of the experiences in literature. Derived from this knowledge a number of lessons could be formulated.

From our beneficial experience with propranolol for IH and the positive results described in literature, it can be concluded that propranolol is currently *the first choice treatment option for airway IHs*. The rapid effect, non-invasive character and superfluity of prolonged corticosteroid treatment, tracheotomy and prolonged periods of intubation, make propranolol superior and less expensive compared to other established treatments.

Of great importance for this patient group is *making the proper diagnosis expeditiously*, so no time is lost before treatment is started. Further investigations can be considered in case of diagnostic doubts like for instance, a biopsy with GLUT1 staining or imaging studies like laryngoscopy, duplex ultrasonography, MRI or CT with contrast. But in case the diagnosis IH is considered, it is worth *starting propranolol right away* before diagnostic procedures have been performed or completed, not wasting time. Associated symptoms, like stridor, diminish within hours, thereby confirming the probability of the diagnosis IH. Regarding the propranolol-dosage, 2 mg/kg/day is generally considered adequate in literature. But in airway IHs doses up to 3 mg/kg/day or even higher are recommended. In part of the patients, reduction of the dosage due to growth of the infant, undeniably resulted in rebound of the symptoms. For many patients, however, usual dosages were also successful.

In conclusion, for this treatment indication, relatively higher propranolol doses seem required, although certain *flexibility considering the treatment dosage* may be obligatory, tailored to the specific patient. Furthermore, because of the risk of rebound swelling, it is important that the treatment is *not discontinued too early*, given the life-threatening symptoms. Therefore, in airway IHs we advise to continue propranolol treatment at least until the age of 15-18 months or even longer.

In the second part of ***Chapter 6***, our anecdotal but promising experience with propranolol for Kaposiform hemangioendothelioma (KHE) has been described.

Kaposiform hemangioendothelioma and tufted angioma (TA) are rare vascular tumors of infancy and early childhood. These are thought to be related entities in the same spectrum of disease.[11,12] Both are associated with Kasabach-Merritt phenomenon (KMP), a consumptive coagulopathy, caused by platelet trapping within the tumor, resulting in a significant decrease in platelet count, characterized by severe thrombocytopenia.[13] In symptomatic KHE, associated with KMP, aggressive treatment is indicated because of the mortality rate from hemorrhagic complications may be as high as 30%.[14,15] Controlled trials on treatment are lacking because of the rare nature of KHE and TA and the variable natural history, sometimes even characterized by spontaneous involution. Complete surgical removal seems the treatment with the best therapeutic outcome, although many tumors are unresectable due to location, extensiveness or tissue infiltration. Several other therapeutic options have been described in literature, often with marginal effect and significant side effects. Vincristine is suggested as first line option, with response rates of 86-100%, but with rare complete resolution, residual lesions,

significant relapse rates and limited use because of side effects like neurotoxicity. In complicated cases often multimodal treatment is applied.[16,17]

The case reported in ***Chapter 6*** describes a 6-week-old male with KHE and KMP treated with propranolol 2 mg/kg/day for 13 months and a total of 4 doses vincristine spread over 4 weeks (67%, 1.5 mg/m^2/wk, once a week). A dramatic response was seen and persisted, also after discontinuation of vincristine after 4 weeks. Moreover, the skin and subcutis recovered remarkably well, with only limited residual lesions despite the previously existing extensive tumor. In literature the average treatment duration of vincristine is 22 weekly courses, in this case reduced to 4 weekly courses. This case therefore illustrates the non-negligible effect of propranolol in KMP. Propranolol is therefore a promising new therapeutic option for KHE and KMP but needs to be defined in further detail in more extensive studies.

7.1.2 Implications for current clinical practice

Before the propranolol-era, treatment of IH was only initiated in case of life-threatening or severe function-threatening cases. Now that the effectiveness of propranolol is becoming increasingly clear, together with increasing experience, *the indication area continues to expand*. With regard to this development, for every treatment indication, the balance between effectiveness and possible side effects has to be evaluated critically. For the majority of the IH patients, treatment is unnecessary and an 'active non-intervention' policy is justified. For some patients treatment is strongly indicated because of a severe function-threatening or even life-threatening IH. For the significant remaining patient group, the consideration about whether or not to treat is much more difficult. For these patients, there is no standardized advice and the decision has to be taken by considering many different determinants e.g.: age, general health, expected growth of the IH and the expected short-term and long-term result from an active approach. But also factors like, expected functional or psychosocial implications of the IH now and for the future, social support, impact of the IH on the parents and the rest of the family and how the parents are facing the IH and the possible treatment, need to be considered. In this phase, but also afterwards, multidisciplinary cooperation and adequately providing information to the parents is essential, in making an adequate decision.

When, after these elaborate considerations, the decision for an active approach with propranolol is taken, it is important that this treatment is tailored to the individual patient, aiming at *personalized medicine*. Regarding the moment of starting treatment, there is a group of patients in which the decision about whether or not to treat can be postponed 1 to 2 weeks, without additional risks, allowing monitoring of growth in this period. On the other hand, in case of an airway IH, it is prudent to start right away, sometimes even without additional investigations to prove the diagnosis.

Regarding the dosage of propranolol, it is important to consider dosage escalation to 3 mg/kg/day in patients with insufficient effect on the conventional dosage of 2 mg/kg/day.[4] In contrast, if side effects occur, it appears that a reduction of the dosage makes successful continuation of treatment possible. Also the duration of treatment is flexible and should be adjusted to the specific patient and treatment indication. In ulcerated IHs, the treatment duration can be shortened (up to 9-12 months of age) but for deep periorbital IHs and airway IHs on the other hand, treatment is advised till the age of 15-18 months.

For the relative large number of IHs with (impending) *ulceration*, propranolol seems *an important contribution to the therapeutic arsenal*. For this indication it is of great importance that propranolol is started as soon as possible, preferable before the onset of ulceration to prevent it. Characteristics of IH, increasing the risk of ulceration should be recognized and anticipated upon: large, segmental IHs, especially localized in the head and neck region, in skin folds but also in the perineum and buttock area. It is however important that in case ulceration occurs, the other components of the treatment triad for ulcerated IH should never be forgotten. Despite the start of propranolol, adequate pain medication and wound care remain crucial in many cases.

With regard to *the initiation of therapy*, for a high-risk patient group initiation of treatment should take place in a clinical setting. High-risk patients are defined as patients younger than 3 months, ex-prematures and patients with comorbid conditions or complications affecting the cardiovascular system, the respiratory system or blood glucose maintenance. For the remaining uncomplicated patient group there is growing evidence that propranolol can be started safely in an outpatient setting, as recently described in a report based on a multidisciplinary and multi-institutional consensus conference.[4] This approach characterized by initiation of treatment and increasing the dosage during day care admissions is currently preferred by the Hecovan-working group.

The parents of all children starting with propranolol, should be counseled about the impact of treatment and the possible side effects. Parents should particularly be aware of the risk of hypoglycemia during fasting, diminished food-intake, gastrointestinal infection and concomitant use of OCS. In this way parents are enabled to recognize and, in some instances, avoid side effects.

Adequate information for all physicians that take care of infants with IH, especially doctors at the infant welfare centre, is important to achieve a paradigm shift in the timing of referral and initiation of treatment of high-risk IHs. In case of timely referral, therapy can be initiated before or early in the proliferation phase, rather than after growth of the IH is completed and complications and/or residual lesions will occur anyway. Low threshold (digital) consultation of specialists on this topic prevents unnecessary visits and more importantly avoids late referrals.

Regarding *the extension of indications*, the beneficial effect of propranolol for KHE is described in this thesis. After our publication, a case series appeared, reporting 11 patients with a wide variety in clinical presentation and therapeutic history, showing that propranolol was not effective in 2/3 of these cases.[18] In case propranolol turned out to be effective, a dosage of 3 mg/kg/day was given. These cases could potentially indicate that propranolol is only effective in a selection of the KHE and TA patients, and a relatively high dose is needed to achieve the desired effect. Future research will probably further explore.

In conclusion, propranolol is a promising new therapeutic modality for a growing patient group with complex IH or other vascular anomalies. The risks and benefits should however be weighed on a case-by-case basis.

7.1.3 Future perspectives

Despite the relative frequency of IH and the potential risk of complications, evidence based international treatment guidelines are missing in literature. An update of the Dutch treatment guideline for IHs, supported by the Dutch support group for patients with hemangioma and vascular anomalies patients and their parents (HEVAS), will however appear in the near future. In general, prospective studies are rare and the available data are clouded by a lack of consensus on treatment criteria and objective outcome measures.

Research on the topic of IH however, flourished in recent years, particularly after the discovery of the efficacy of propranolol, which has brought a revolutionary shift in IH treatment with major implications for clinical practice. This shift to beta-blockade in the treatment of IH is also mainly based on observational studies and expert opinions. Nevertheless, the studies outlined in this thesis and the accumulating experience and evidence in literature comprise a large number of propranolol-treated patients, showing a relative uniformity in results, supporting the undisputed beneficial effect of beta-blocker treatment for this complex patient group. In literature, two randomized controlled trials have been described (propranolol versus placebo), confirming the effectiveness of propranolol.[19,20] The excellent efficacy of propranolol in combination with a favorable side effect profile, compared to earlier treatments like OCS, made randomized controlled trials to support these findings however almost unwarrantable. *'Real clinical practice data'*, as described in this thesis are therefore obligatory to define the indication area and other characteristics of the treatment regimen, which are necessary, to ensure optimal effective and safe clinical practice.

Detailed *prospective studies with longer follow-up* are an important future goal, in the first place to identify the long-term safety profile of propranolol for these indications. In May 2013, during a scientific meeting on 'Controversies in Vascular Anomalies' in New York, there was concern about the long term effect of propranolol on the developing brain. Based on animal studies, it was hypothesized that the emotional memory can be affected

by the diminished formation of beta-adrenergic regulated connection between amygdala and hippocampus.[21] This can be only tested once the child is 5 year of age or older. The possible future implications of this potential side effect have to be investigated and this illustrates *yet again* the importance of prospective follow-up studies on long-term safety. Moreover, it emphasizes that initiation of propranolol should be limited to complicated IHs and that the indication area should not be extended by now.

With upcoming information on long-term results, optimalisation of treatment protocols will facilitate to establish the optimal duration of treatment and the most favorable reduction schedules tailored to the specific IH patient, in order to minimize the risk of relapse.

Furthermore the dosage schedule may be even better matched to the specific IH patient, with some patients starting dosages higher or lower than the standard dosage of 2 mg/kg/day. Several studies suggesting a reduction of the initial dose for a specific patient population have already been described, particularly in order to reduce side effects.[22-25] More extensive studies are needed to refine these results.

Besides oral propranolol, the position of the *topical beta-blocker timolol* (timolol maleate ophthalmic solution 0.5% or gel forming solution (GFS) 0.1%, 0.25% or 0.5%) has been explored in recent years and seems especially effective for small, superficial IHs.[26-34] The role of this topical application for deep or mixed type IHs seems limited, according to limited permeability. The systemic absorption seems also limited, but the pharmacokinetics for this therapeutic mode are poorly defined.[35,36] It is important to be cautious when using topical timolol in large, ulcerated, mucosal or perimucosal IHs, where the skin barrier is compromised and when occlusion is likely (e.g. diaper area), because the percutaneous absorption may be larger in these cases. For these patient groups however, treatment with oral propranolol is generally a better choice. In order to prevent delay in starting systemic propranolol, the indication for topical treatment must be considered carefully and therapeutic effect of topical timolol application has to be monitored accurately during the growth phase of the IH. Future trials will provide more clarity in the characteristics and indication profile of this topical variant of beta-blocker therapy.

The discovery of beta-blockade as an effective mechanism in the treatment of IH has also given an impulse to the research in cell biology of IH and recently resulted in the finding of expression of components of the RAS by the endothelium of this proliferating vascular tumor. The additional assumption that beta-blockers mediate their effect in IH by modulation of the RAS through inhibition of the renin activity, probably creates possibilities in the use of alternative and perhaps *more targeted treatments* for this indication.[37] A few reports recently described casuistic experiences with ACE-inhibitors (captopril) and other, beta-blockers like atenolol, acebutolol and nadolol[38-42] These other therapeutic approaches, modulating RAS, need to prove their added value in future research. Further investigations may also elucidate novel pathways for the RAS in the developmental

biology of microvasculature in general, with potentially useful implications for regenerative medicine and tumor biology.

In daily clinical practice and clinical research concerning the role of propranolol and upcoming related therapies in the treatment of IH, there is a growing need for accurate and objective outcome measurement. In the past years several scoring systems have been developed for the measurement of severity, complications and proliferative activity of IH.[43,44] Accurate volume measurement is however missing and is of utmost importance in the assessment of the IH with respect to the risk of complications and/or residual lesions. The existing bedside techniques and imaging studies were in general inappropriate for volume measurement in IH.[5-8,45,46] A new technique for this purpose is *3D stereophotogrammetry*. This technique is adequate and promising, but the applicability needs to be further explored in future more extensive research.

After the identification of the endothelial expression of beta-2 adrenergic receptors in IH, the expression of these receptors on several other vascular anomalies is being explored and the investigation of the possible *expansion of the indications* has started.[47,48] After the treatment of KHE and KMP described in this thesis and subsequent case series, the efficacy of propranolol was explored in case reports and small case series for lymphatic malformations, with varying results.[18,49,50] In order to specify the possible expansion of the indication area of propranolol, further and more extensive research is required.

In addition to the effect of beta-blockade on IH and other vascular anomalies, the role of the carcineurin inhibitor *sirolimus* (Rapamycin) has been investigated. The target of this treatment is a kinase of the phosphoinositide 3-kinase signaling pathway; one of the most important intracellular mediators of the activity of growth factor receptors like VEGF.[51,52] The potential toxicity appears to be greater than that of propranolol and well designed studies assessing the effect of treatment for IH are lacking.[53]

7.1.4 Conclusion

The discovery of the role of beta-blockade in the treatment of IH has not only changed the routine management of this vascular tumor, but also gives clues to new treatments related to the insight into this mode of action. In current clinical practice, propranolol is the first choice treatment for patients with a complicated IH.

Development of treatments particularly targeting the RAS may provide innovative treatment-opportunities with a favorable efficacy-safety ratio for the patients of tomorrow. Further research on the pathomechanism behind IH may provide important new treatment options for diseases caused by dysregulation of angiogenesis

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8

8.1 Summary

Infantile hemangiomas (IHs) are the most common soft-tissue tumors of infancy. Because they involute spontaneously after a period of disproportionate growth, most have little consequences. A significant portion however has the potential to result in complications of concern. For the past decades, high-dose oral corticosteroids (OCS) were the first-choice therapy for this patient category despite significant treatment failure and serious side effects. After the serendipitous discovery of the beneficial effect of beta-blockade on IH in 2008, the treatment of this complicated patient group changed revolutionary.

This thesis aims to obtain more insight into complicated IH. Moreover, the implications of the changing landscape of treatment options after the discovery of propranolol are further explored. The five major aims of this thesis are:

Aim 1: To explore the indication area and treatment regimen of propranolol in infantile hemangioma.

Aim 2: To get more insight in the role of propranolol in the treatment of ulceration, the most common complication of infantile hemangioma.

Aim 3: To enlarge knowledge about quality of life aspects in patients with infantile hemangioma and their families, especially with respect to different treatment modalities.

Aim 4: To explore the future role of quantitative imaging analysis, in particular 3D-stereophotogrammetry in the follow-up of infantile hemangioma growth and regression.

Aim 5: To investigate and describe the broader applicability of propranolol in vascular tumors.

In ***Chapter 1***, a general introduction is given on IH, followed by an overview of the different complications of IH and indications for their treatment. Finally, the management and treatment options are outlined with special attention to beta-blockade and propranolol. Subsequently the aims of this thesis are formulated.

In ***Chapter 2***, the experiences of the Hecovan-working group with the first 174 patients treated with propranolol for complicated IHs are described in a prospective way. For 99.4% of the patients, propranolol treatment could be classified as successful within 3 weeks, defined by fading and softening of the tumor with reduction of swelling, improvement of ulceration or disappearance of symptoms in case of airway IH. With regard to the treatment regimen, it could be concluded that a certain degree of flexibility according to the dosages

and treatment duration is obligatory in order to achieve the optimal therapeutic result with minimal adverse events. The reported adverse events in this cohort were in general mild, reversible and dose-dependent.

Concerning the treatment-start, initiation of treatment and increase to the target dosage should be carried out in a clinical setting for high-risk patients. For the remaining uncomplicated patient group, the Hecovan-working group prefers cardiovascular monitoring during daycare admissions, after the initial dose and after significant dose increase (>0.5 mg/kg/day), in this phase of research.

In the first part of ***Chapter 3***, a retrospective analysis is performed, investigating the differences between ulcerated and non-ulcerated IHs. Larger IHs with a superficial component, predominantly localized in the head-neck region and diaper area are more at risk for ulceration. Ulceration most frequently occurred during the proliferation phase of the IH. In addition, patients with ulcerated IHs were significantly more often born prematurely. These characteristics of the IH and prematurity are important factors in the consideration of whether or not to start treatment.

In the second part of chapter 3 a retrospective study is described, in which the role of propranolol for patients with ulcerated IH is explored. Twenty patients with an ulcerated IH treated with propranolol were compared with a historical control group. The propranolol-treated patients had a significantly shorter ulceration time and moreover initiation of propranolol earlier in the proliferation phase nearly always resulted in a tendency to faster healing. In view of the risk profile for ulceration outlined in the first part of chapter 3, it is therefore probably the best choice to start propranolol early in an IH with characteristics prone for future ulceration.

Chapter 4 presents a retrospective study exploring the impact and contentment with treatment for propranolol-treated IH patients and their parents compared with a matched patient group treated with OCS. During treatment, parents from the OCS group felt significantly more worried and insecure in general. Additionally, parents from the propranolol group perceived less negative influence on normal life issues and gave a higher quality of life (QoL)-score for both the periods during and after treatment. In general, it seems that propranolol diminishes the impact of IH as a condition and, for the parents, improves the impact of treatment and the quality of life.

In ***Chapter 5***, a pilot study is described, in which the role of 3D stereophotogrammetry for the measurement of volume changes in facial IH is explored. To obtain data, a registration procedure was used, characterized by volume subtraction of digitalized photographs at two times. This technique could be used in two different ways. Images were either superimposed (method 1) or mirrored with the unaffected side of the face (method 2). With both methods the volumetric difference at two different times was calculated. In

general, 3D stereophotogrammetry is a new, promising, non-invasive and accurate method in volume measurement of IHs. It is expected that if the measuring points are closer together in time, both methods may be suitable and accurate, but method 1 is more basic and generally applicable. In case of long time intervals between the different measuring points, the second method seems more suitable, because it corrects for the growth of the child.

In the first part of ***Chapter 6***, the role of propranolol for airway IHs is described based on a case series and an overview of the experiences in literature. Propranolol turned out to be a rapidly effective and safe treatment strategy for most airway-comprising IHs and should be the first-choice treatment for airway IHs at this time. Despite the efficacy of propranolol in the majority of the patients, OCS or intralesional steroids were often started primarily, unfortunately with insufficient effect. Of great importance for this patient group is making the proper diagnosis expeditiously, so no time is lost before treatment is started. In case IH is in the differential diagnosis, it is worth considering initiation of propranolol right away, before (invasive) diagnostic procedures have been performed. The effect on the symptoms can be already noticeable within one day after starting treatment. Also for this treatment indication, a certain flexibility regarding the treatment dosage may be obligatory, because in some cases a relative higher propranolol target dosage was required. Finally, it is important that the treatment is not discontinued too early, given the potential complications of relapse.

In the second part of chapter 6, a patient with Kaposiform hemangioendothelioma (KHE) and Kasabach-Merritt phenomenon (KMP) is described, treated with propranolol and a total of 4 weekly doses vincristine. A dramatic response was seen and persisted, also after discontinuation of vincristine. In literature, the average treatment duration of vincristine is 22 weekly courses, in this case reduced to 4 weekly courses. This case illustrates the non-negligible effect of propranolol in KMP. Propranolol is therefore a promising new therapeutic option for KHE and KMP but needs to be defined in further detail in more extensive studies.

In ***Chapter 7***, the aims of this thesis are discussed in the light of the findings described in the studies in chapter 2-6. Moreover, recommendations for further clinical research are outlined and viewpoints for future developments are revealed.

8.2 Samenvatting

Infantiele hemangiomen (IH) zijn de meest voorkomende weke-delen tumoren op de kinderleeftijd. Omdat het natuurlijke beloop, na een periode van disproportionele groei, gekenmerkt wordt door spontane involutie, worden er bij de meeste patiënten geen grote problemen gezien. Een deel gaat echter wel gepaard met zorgelijke complicaties. De behandeling van eerste keuze voor deze groep patiënten was de afgelopen decennia het toedienen van hoge doses orale corticosteroïden (OCS), ondanks het beperkte resultaat en serieuze bijwerkingen.

Na de serendipiteuze ontdekking van het gunstige effect van beta-adrenerge blokkade op IH in 2008, is de behandeling van deze gecompliceerde patiëntengroep revolutionair veranderd.

Dit proefschrift beoogt meer inzicht te verschaffen in gecompliceerde IH. Daarnaast worden de implicaties van het veranderende landschap van behandelingsmogelijkheden na de ontdekking van propranolol verder onderzocht. De vijf belangrijkste doelstellingen van dit proefschrift zijn:

Doelstelling 1: Het onderzoeken van het indicatiegebied en het behandelprotocol van propranolol voor infantiele hemangiomen.

Doelstelling 2: Meer inzicht verwerven in de rol van propranolol bij de behandeling van ulceratie, de meest voorkomende complicatie van infantiele hemangiomen.

Doelstelling 3: Het inzicht vergroten in de kwaliteit van leven aspecten van patiënten met een infantiel hemangioom en hun families, in het bijzonder rondom de verschillende behandelingsmodaliteiten.

Doelstelling 4: De toekomstige rol van kwantitatieve beeldanalyse verkennen, in het bijzonder 3D fotografie, in de follow-up van groei en regressie van infantiele hemangiomen.

Doelstelling 5: Het onderzoeken en beschrijven van de bredere toepasbaarheid van propranolol voor vasculaire tumoren.

In ***Hoofdstuk 1*** wordt een algemene inleiding gegeven over IH, gevolgd door een overzicht van de verschillende complicaties en behandelindicaties. Vervolgens worden de verschillende behandelmogelijkheden voor IH uiteengezet, met het accent op beta-adrenerge blokkade en propranolol. Tot slot worden de doelstellingen van dit proefschrift geformuleerd.

In ***Hoofdstuk 2*** wordt een prospectieve analyse beschreven van de ervaringen van de Hecovan-werkgroep met de eerste 174 patiënten die werden behandeld met propranolol in verband met een gecompliceerd IH. Voor 99.4% kon deze behandeling worden aangemerkt als succesvol binnen 3 weken, gedefinieerd als het lichter en zachter worden van de tumor, met vermindering van zwelling, verbetering van ulceratie en verdwijnen van symptomen in geval van luchtwegbetrokkenheid. Met betrekking tot het behandelprotocol, kon er geconcludeerd worden dat er een zekere flexibiliteit noodzakelijk is ten aanzien van de doseringen en behandelduur. Dit om het optimale therapeutische resultaat te bereiken met zo weinig mogelijk bijwerkingen. In ons cohort waren de gerapporteerde bijwerkingen in het algemeen mild, reversibel en dosisafhankelijk.

Wat betreft de start van de behandeling, dient voor hoogrisico patiënten het opstarten en het ophogen naar de streefdosering plaats te vinden in een klinische setting. Voor de resterende ongecompliceerde patiëntengroep, heeft opstart van propranolol met cardiovasculaire monitoring tijdens dagopnames, na de eerste dosering en na significante ophoging van de dosering (>0.5 mg/kg/dag), de voorkeur van de Hecovan-werkgroep, in deze fase van onderzoek.

In het eerste deel van ***Hoofdstuk 3*** is een retrospectieve analyse beschreven, waarbij het verschil tussen ulcererende en niet-ulcererende IH wordt beschreven. Er kon geconcludeerd worden dat grote IH, met een superficiële component, met name gelokaliseerd in het hoofd-hals gebied en luiergebied, frequenter ulcereerden. Ulceratie trad meestal op tijdens de proliferatiefase van het IH. Patiënten met een ulcererend IH waren significant vaker prematuur geborenen. Deze eigenschappen van het IH of de IH-patiënt zijn belangrijk in de overweging om wel of niet over te gaan tot behandeling.

In het tweede deel van hoofdstuk 3 wordt een retrospectieve studie beschreven waarin de rol van propranolol in de behandeling van ulceratie werd onderzocht. Twintig met propranolol behandelde patiënten met een ulcererend IH werden vergeleken met een historische controlegroep. Het bleek op de eerste plaats dat de propranolol-patiënten een significant kortere ulceratietijd hadden en bovendien dat het opstarten van propranolol vroeg in de proliferatiefase bijna altijd resulteerde in een tendens tot snellere genezing. Met betrekking tot het risicoprofiel voor ulceratie weergegeven in het eerste deel van hoofdstuk 3, is het waarschijnlijk de beste keuze om propranolol vroeg in de proliferatiefase te starten voor IH met een hoog risico op ulceratie.

In ***Hoofdstuk 4*** wordt een retrospectieve studie beschreven, waarin de impact van de behandeling en de tevredenheid met de behandeling werd onderzocht voor een groep met propranolol behandelde patiënten en hun ouders. Deze gegevens werden vervolgens vergeleken met de gegevens van een overeenkomstige historische controlegroep die behandeld was met OCS. Ouders van patiënten in de OCS groep maakten zich tijdens de behandelingsperiode significant meer zorgen en voelden zich onzekerder. De ouders in

de propranolol groep ondervonden significant minder negatieve invloed op algemene dagelijkse bezigheden en gaven een hogere kwaliteit van leven score voor zowel de periode tijdens als na de behandeling. In het algemeen lijkt propranolol de impact van het IH te verminderen en, voor de ouders, de impact van behandeling gunstig te beïnvloeden, alsmede de kwaliteit van leven.

In ***Hoofdstuk 5*** wordt er een pilotstudy beschreven waarin de rol van 3D fotografie voor de meting van volumeveranderingen van faciale IH werd onderzocht. Om data te verkrijgen werd er een registratieprocedure toegepast, gekenmerkt door volume subtractie van digitale foto's op verschillende meetmomenten. Deze techniek kon gebruikt worden op twee verschillende manieren waarin beelden respectievelijk over elkaar geprojecteerd werden (methode 1) of gespiegeld werden met het niet-aangedane deel van het gelaat (methode 2). Met beide methoden kon het verschil in volume op twee verschillende tijdstippen berekend worden. In het algemeen kan er geconcludeerd worden dat 3D fotografie en nieuwe, veelbelovende, niet invasieve en nauwkeurige methode is in de volumemeting van IH. Wanneer de meetpunten dicht bij elkaar liggen, lijken beide methoden geschikt en nauwkeurig, maar methode 1 is eenvoudiger en breder toepasbaar. In geval van langere intervallen tussen de verschillende meetmomenten, lijkt methode 2 meer geschikt omdat deze corrigeert voor de groei van het kind.

In het eerste deel van ***Hoofdstuk 6***, wordt de rol van propranolol voor luchtweg IH beschreven, gebaseerd op een serie van vijf casus en een overzicht van de ervaringen beschreven in de literatuur. Propranolol blijkt een snelle, effectieve en veilige behandeling te zijn voor de meeste luchtwegbedreigende IH en zou de eerste keuze behandeling voor luchtweg IH op dit moment moeten zijn. Ondanks het effect van propranolol bij de meerderheid van de patiënten, werden orale of intralesionale steroïden vaak in eerste instantie gestart, echter vaak met onvoldoende resultaat. Van groot belang voor deze patiëntengroep is dat de diagnose snel gesteld wordt, zodat er geen tijd verloren gaat voordat de behandeling wordt gestart. Voor de patiënten waarbij een IH differentiaal diagnostisch wordt overwogen, is het de moeite waard om meteen met propranolol te starten zonder tijd te verliezen met (invasieve) diagnostische procedures, omdat het effect op de symptomen al binnen een dag merkbaar kan zijn. Ook voor deze behandelingsindicatie is het van belang dat er een zekere flexibiliteit ten aanzien van de behandeldosering in acht wordt genomen, omdat in sommige gevallen een hogere streefdosering noodzakelijk bleek te zijn. Tot slot is het van belang dat de behandeling niet te snel wordt gestaakt, gezien het potentiële risico op complicaties in geval van recidief zwelling.

In het tweede deel van hoofdstuk 6 wordt een patiënt met Kaposiform hemangioendothelioom (KHE) en het Kasabach-Merritt fenomeen (KMP) beschreven, die werd behandeld met propranolol in combinatie met in totaal 4 wekelijkse doseringen vincristine. Een indrukwekkende respons werd gezien welke persisteerde, ook nadat de vincristine

was afgebouwd. In de literatuur is de gemiddelde behandelduur met vincristine 22 weken; in deze casus kon de behandelduur dus worden gereduceerd tot 4 wekelijkse doseringen. De casus illustreerde het niet te verwaarlozen effect van propranolol voor KHE/ KMP. Propranolol is daarom een veelbelovende nieuwe therapeutische optie voor KHE en KMP. Deze rol dient echter verder onderzocht te worden in grootschaliger onderzoek.

In ***Hoofdstuk 7*** worden de antwoorden op de doelstellingen van dit proefschrift geformuleerd in het licht van de studies die beschreven zijn in hoofdstuk 2 tot en met 6. Verder worden er aanbevelingen gedaan voor verder klinisch onderzoek en worden er gezichtspunten voor toekomstige ontwikkelingen gesuggereerd.

8.3 List of publications

Related to the thesis

Hermans DJJ, Boezeman JB, Van de Kerkhof PCM, Rieu PN, van der Vleuten CJM. Differences between ulcerated and non-ulcerated hemangiomas, a retrospective study of 265 cases. *Eur J Dermatol.* 2008; 19(2):152-6.

Hermans DJJ, van Beynum IM, van der Vijver RJ, Schultze Kool LJ, de Blaauw I, van der Vleuten CJM. Kaposiform hemangioendothelioma with Kasabach-Merritt syndrome: a new indication for propranolol treatment. *J Pedriat Hematol Oncol.* 2011; 33(4): 171-3.

Hermans DJJ, van Beynum IM, Schultze Kool LJ, van de Kerkhof PCM, Wijnen MH, van der Vleuten CJM. Propranolol, a very promising treatment for ulceration in infantile hemangiomas: a study of 20 cases with matched historical controls. J Am Acad Dermatol. 2011; 64(5): 833-8.

Hermans DJJ, Bauland CG, Zweegers J, van Beynum IM, van der Vleuten CJM. Propranolol in a case series of 174 patients with complicated infantile haemangioma: indications, safety and future directions. *Br J Dermatol.* 2013; 168(4): 837-843.

Hermans DJJ, Zweegers J, Evers AWM, van der Vleuten CJM. Parental experiences with propranolol versus oral corticosteroids for complicated infantile hemangioma, a retrospective questionnaire study. *Eur J Dermatol.* (2013) *Accepted*

Hermans DJJ, Maal TJJ, Bergé SJ, van der Vleuten CJM. Three-dimensional stereophotogrammetry: a novel method in volumetric measurement of infantile hemangioma. *Pediat Dermatol. (2013) In press*

Broeks IJ, Hermans DJJ, Dassel ACM, van der Vleuten CJM, van Beynum IM. Propranolol in life-threatening airway hemangioma: a case series and review of literature.
Int J Pediat Otorhinolaryngol. (2013) *In press*

Not related to the thesis

Hermans DJJ, Beretty PJM. Een vrouw met een klein wondje onder haar borst. *Ned Tijdschrift Derm Ven.* 2009; 19(10): 623.

Van der Vleuten CJM, Hermans DJJ, Schultze Kool LJ, Kroese-Deutman HC, Aronson DC, van Beynum IM. Propranolol, de panacee voor bedreigende hemangiomen in de groeifase? De behandeling van hemangiomen met propranolol. *Ned Tijdschrift Derm Ven.* 2010; 20(1): 8-11.

Van Beynum IM, Bauland CG, Smit J, Hermans DJJ, van der Vleuten CJM. *De praktische behandeling van hemangiomen.* Praktische Pediatrie. 2010; 4(4): 246-249.

Hermans DJJ, Ottenhof M, Wijnen MH, van Beynum IM, van der Horst MA, van der Vleuten CJM. Behandeling van infantiele hemangiomen met propranolol, goede resultaten en weinig bijwerkingen. *Ned Tijdschr Geneeskd.* 2011; 155(40): 1793-1801.

8.4 Curriculum Vitae

Denise Josephina Johanna Hermans werd op 23 december 1982 geboren in Roermond en groeide op in Maasbracht. Na het behalen van haar VWO diploma aan het Bisschoppelijk college Echt in 2001 begon zij aan haar studie geneeskunde aan de Katholieke Universiteit Nijmegen (nu geheten Radboud Universiteit Nijmegen). Deze studie sloot zij in 2007 af, met een wetenschappelijke stage, met als onderwerp 'ulcererende hemangiomen' op de afdeling dermatologie aan de Radboud Universiteit Nijmegen, onder begeleiding van dr. Carine J. M. van der Vleuten. Na een jaar als arts assistent niet in opleiding gewerkt te hebben op de afdeling dermatologie van het Catharina ziekenhuis in Eindhoven, begon zij in mei 2008 aan de opleiding tot dermatoloog, in het UMC St. Radboud. Tijdens haar opleiding werkte zij aan dit promotie onderzoek naar gecompliceerde hemangiomen en de rol van de behandeling met propranolol. Na het afronden van haar opleiding in november 2013 zal zij als dermatoloog gaan werken in het Jeroen Bosch ziekenhuis in Den Bosch en tevens verbonden blijven als parttime staflid aan de afdeling dermatologie van het UMC St. Radboud.

8.5 Dankwoord

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